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ATTN: PCT BRANCH

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Makoto TAKEUCHI, Ryo NAITO, Masahiko HAYAKAWA, Yoshinori OKAMOTO, Yasuhiro YONETOKU, Ken IKEDA and Yasuo ISOMURA

Serial No.: 08/860,377   PCT/JP95/02713, filed December 27, 1995

Filed: June 25, 1997

For: NOVEL QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITION THEREOF

SUBMISSION OF EXECUTED DECLARATION

ATTN: PCT BRANCH
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the "Notification of Missing Requirements Under 35 U.S.C. 371 in the United States Designated/Elected Office (DO/EO/US)", mailed July 31, 1997, submitted herewith is the Declaration for the above-mentioned application properly executed by the inventors. Also enclosed please find an executed Assignment and PTO Form 1595.

Checks for the statutory fee of $ 130.00 and Assignment recordation fee of $ 40.00 are attached. You are also directed and authorized to charge or credit any difference or overpayment to Deposit Account No. 19-4880. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. 1.16 and 1.17 which may be required during the entire pendency of the application to Deposit Account No. 19-4880. A duplicate copy of this transmittal letter is attached.

Respectfully submitted,

Waddell A. Biggart
Registration No. 24,861

SUGHRUE, MION, ZINN, MACPEAK & SEAS
2100 Pennsylvania Avenue, N.W.
Washington, D.C. 20037-3202
Tel: (202) 293-7060
WAB:tjs

Date: August 28, 1997

LAW OFFICES
SUGHRUE, MION, ZINN, MACPEAK & SEAS
2100 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, D.C. 20037-3202

TELEPHONE
(202) 293-7060

TELEX
6491103

FACSIMILE
(202) 293-7860
(202) 293-9131

JAPAN OFFICE
TOEI NISHI SHIMBASHI BUILDING 4F
13-5 NISHI SHIMBASHI 1-CHOME
MINATO-KU, TOKYO 105 JAPAN
TELEPHONE (03) 3 503-3760
FACSIMILE (03) 3 503-3756

June 25, 1997

ATTN: BOX PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

Re: Application of **Makoto TAKEUCHI, Ryo NAITO, Masahiko HAYAKAWA, Yoshinori OKAMOTO, Yasuhiro YONETOKU, Ken IKEDA and Yasuo ISOMURA**
NOVEL QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITION THEREOF
Our Reference: Q45752
PCT/JP95/02713, filed December 27, 1995

Dear Sir:

Applicants herewith submit the attached papers for the purpose of entering the National stage under 35 U.S.C. § 371 and in accordance with Chapter II of the Patent Cooperation Treaty. Attached hereto is the application identified above which is a translation **of PCT International Application No. PCT/JP95/02713, filed December 27, 1995**, comprising the specification, claims, International Prelimimary Examination Report, Attachment A-1 and A-2 (copy of Japanese with English language translation of Abstract as amended and published), Attachment B-1 and B-2 (copy of Japanese with English language translation of amendments made after international publication), Attachment C-1 and C-2 (copy of Japanese with English language translation of explanation of reasons for amendments), International Search Report and Preliminary Amendment. **The executed Declaration and Power of Attorney and Assignment will be submitted at a later date.**

The Government filing fee is calculated as follows:

Total Claims	14 - 20 =	0 x $22 =	$ 000.00
Independent Claims	2 - 3 =	0 x $80 =	$ 000.00
Base Filing Fee	($910.00)		$ 910.00
Multiple Dep. Claim Fee	($260.00)		$ 260.00
TOTAL FILING FEE			**$1170.00**

A check for the statutory filing fee of $ **1,170.00** is attached. You are also directed and authorized to charge or credit any difference or overpayment to Deposit Account No. 19-4880. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. 1.16 and 1.17 which may be required during the entire pendency of the application to Deposit Account No. 19-4880. A duplicate copy of this transmittal letter is attached.

Priority is claimed from:

Japanese Patent Application	Filing Date
Hei-6-327045	December 28, 1994

Respectfully submitted,
SUGHRUE, MION, ZINN, MACPEAK & SEAS
Attorneys for Applicant(s)

By: Waddell A Biggart
Waddell A. Biggart
Reg. No. 24,861

WAB:tjs

ATTN: BOX PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Makoto TAKEUCHI, Ryo NAITO, Masahiko HAYAKAWA, Yoshinori OKAMOTO, Yasuhiro YONETOKU, Ken IKEDA and Yasuo ISOMURA

Serial No.: NOT YET ASSIGNED PCT/JP95/02713, filed December 27, 1995

Filed: June 25, 1997

For: NOVEL QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITION THEREOF

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Prior to examination of the above-identified application, please amend the above-mentioned application as follows:

IN THE SPECIFICATION:

Page 1, line 8, delete ", N-oxides".

Page 4, line 13, delete ", N-oxides".

Page 6, line 23, delete ", N-oxides".

Page 7, line 11, delete ", N-oxides";

line 20, delete ", N-oxides"; and

line 25, delete ", N-oxides".

Page 8, line 2, delete ", N-oxides";

line 5, delete ", N-oxides"; and

line 8, delete ", N-oxides".

Page 23, line 1, delete "affinity" and insert --binding--.

Page 24, line 2, delete "affinity" and insert --binding--.

Page 27, line 11, delete "affinity" and insert --binding--.

Page 78, Table 28, Compound No. B-158, Ring A, delete "$_nC_2H_7$" and insert --$_nC_3H_7$--.

IN THE CLAIMS:

Claim 1, page 85, line 13, delete ", an N-oxide thereof,".

Claim 2, page 85, lines 1-2, delete ", an N-oxide thereof".

Claim 3, page 86, lines 1-2, delete ", an N-oxide thereof".

Claim 4, page 86, lines 1-2, delete ", an N-oxide thereof".

Claim 5, page 87, lines 1-2, delete ", an N-oxide thereof".

Claim 6, page 87, lines 1-2, delete ", an N-oxide thereof".

Claim 7, page 87, lines 1-2, delete ", an N-oxide thereof".

Claim 8, page 87, lines 1-2, delete ", an N-oxide thereof".

Claim 9, page 90, line 1, delete ", an N-oxide".

IN THE ABSTRACT:

Page 91, line 10, delete ", N-oxides".

REMARKS

The above amendments are made for editorial purposes.

No questions of new matter should arise and entry is requested.

Respectfully submitted,

Waddell A. Biggart
Registration No. 24,861

SUGHRUE, MION, ZINN, MACPEAK & SEAS
2100 Pennsylvania Avenue, N.W.
Washington, D.C. 20037-3202
Tel: (202) 293-7060
WAB:tjs

Date: June 25, 1997

Specification

NOVEL QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITION THEREOF

Technical Field

This invention relates to medicines, particularly quinuclidine derivatives or their salts, N-oxides or quaternary ammonium salts having muscarinic receptor antagonistic activities and also to pharmaceutical compositions containing such compounds.

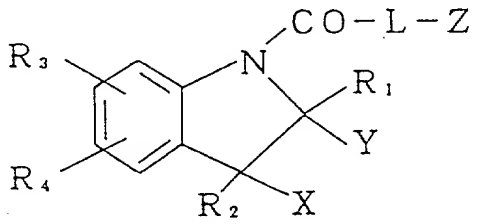
Background Art

Studies have been made on the muscarinic receptor, and it is known that compounds having muscarinic receptor antagonistic activities cause bronchodilation, suppression of gastrointestinal motility, suppression of acid secretion, dry mouth, mydriasis, suppression of bladder contraction, hypohidrosis, tachycardia, or the like. It is known that the muscarinic receptor includes at least three subtypes. The M_1 receptor mainly exists in the brain or the like, the M_2 receptor in the heart or the like, and the M_3 receptor in the smooth muscles or gland tissues.

A number of such compounds having muscarinic receptor antagonistic activities are hitherto known and, for example, atropine is a typical example ("The MERCK INDEX, ELEVENTH EDITION", p. 138). However, atropine antagonizes the M_1, M_2

and M_3 receptors non-selectively, so that it is difficult to use it for the treatment of a specific disease. In recent years, according to the progress of the studies on the subtypes of the muscarinic receptor, compounds having selective antagonistic activities against the M_1, M_2 or M_3 receptor have been investigated (an unexamined published British Patent Application No. 2,249,093, an unexamined published Japanese Patent Application (*kokai*) 1-131145, and an unexamined published Japanese Patent Application (*kokai*) 3-133980). There is a demand for a compound having selective antagonistic activity against muscarinic M_3 receptor among these three subtypes and is free from the cardiac side effects resulting from the M_2 receptor.

The compound represented by the following general formula is described in an unexamined published Japanese Patent Application (*kokai*) 62-252764.

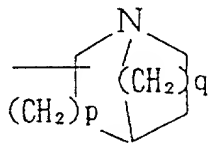


(wherein L represents NH or O;

X and Y each independently represents a hydrogen atom or a C_{1-6} alkyl group or they may be combined together to form a bond;

R_1 and R_2 each independently represents a hydrogen atom, a C_{1-6} alkyl group ...(omission)... ;

R_3 and R_4 each independently represents a hydrogen atom, a halogen atom, CF_3, a C_{1-6} alkyl group ...(omission)..., a phenyl group, an amino group which may optionally be N-substituted by one or two groups selected from phenyl, C_{1-6} alkyl groups or may optionally be N-disubstituted by C_{6-8} polyethylene... (omission)...;

Z represents  or the like;

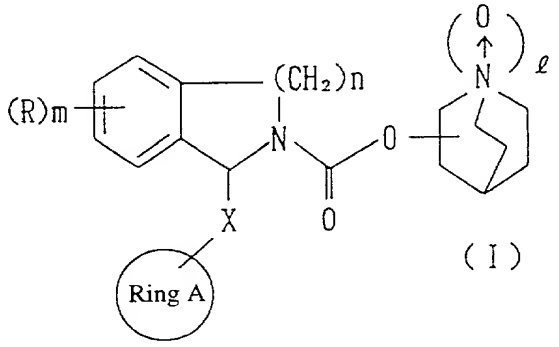
p is 1 or 2; and q is 1-3.

The compound described in the above patent literature is disclosed as a 5-HT antagonist and no disclosure about the muscarinic receptor antagonistic activity is found. The above compound is clearly distinguished from the compound according to the present invention in pharmacological effects.

Disclosure of the Invention

The inventors of the present application have carried out extensive studies on compounds having the above-described muscarinic M_3 receptor antagonistic activities. As a result, we created novel quinuclidine derivatives having a basic skeleton different from that of the conventional compound, and found that such compounds have excellent selective antagonistic activity against muscarinic M_3 receptor, resulting in the completion of the present invention.

Thus, the compounds of the present invention relate to quinuclidine derivatives represented by the following general formula (I); their salts, N-oxides or quaternary ammonium salts; pharmaceutical compositions comprising said compounds or salts thereof and pharmaceutically acceptable carriers, particularly to muscarinic M_3 receptor antagonists.



(I)

(symbols in the formula have the following meanings:

Ring A: an aryl group, a cycloalkyl group, a cycloalkenyl group, a heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, wherein said ring may be substituted by an optional substituent;

X: a single bond or a methylene group;

R: a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group or a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group;

ℓ: 0 or 1,

m: 0 or an integer of 1 to 3, and

n: an integer of 1 or 2, hereinafter the same apply similarly)

Among the compound (I) of the present invention, particularly preferred compounds are quinuclidine derivatives wherein the ring A represents an aryl group, a cycloalkyl group, a cycloalkenyl group, a heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, in which such a ring may be substituted by a substituent selected from the group consisting of a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group, and a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group, and their salts, N-oxides or quaternary ammonium salts;

quinuclidine derivatives wherein R represents a halogen atom, a lower alkyl group, a hydroxyl group, a lower

alkoxy group, a nitro group, a cyano group, an amino group or a mono- or di-lower alkylamino group, and the ring A represents an aryl group, a cycloalkyl group, a cycloalkenyl group, a 5- or 6-membered monocyclic heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, in which such a ring may be substituted by a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group, a nitro group, a cyano group, an amino group or a mono- or di-lower alkylamino group, and their salts, N-oxides or quaternary ammonium salts;

quinuclidine derivatives wherein m is 0, and the ring A represents an aryl group, a cycloalkyl group or a cycloalkenyl group which may be substituted by a halogen atom, a lower alkyl group, a hydroxyl group or a lower alkoxy group, or a 5- or 6-membered monocyclic heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, and their salts, N-oxides or quaternary ammonium salts;

quinuclidine derivatives wherein the ring A represents a phenyl group which may be substituted by a halogen atom or a lower alkyl group, a cycloalkyl group, a pyridyl group, a furyl group or a thienyl group, and their salts, N-oxides or quaternary ammonium salts;

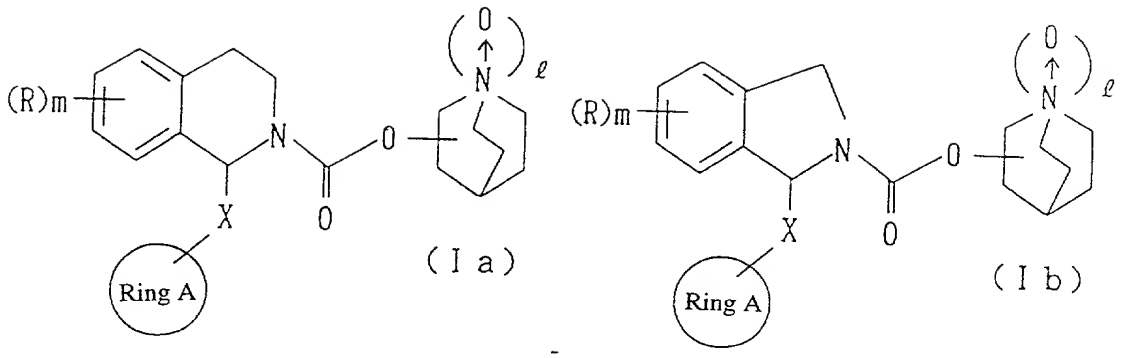
quinuclidine derivatives wherein X represents a single bond, and their salts, N-oxides or quaternary ammonium salts; and

quinuclidine derivatives wherein n is 2, and their salts, N-oxides or quaternary ammonium salts.

The present invention also provides muscarinic M_3 receptor antagonists which comprise quinuclidine derivatives (I) or their salts, N-oxides or quaternary ammonium salts, that is, the compound (I) of the present invention and pharmaceutically acceptable carriers, preferably agents for the prevention and/or treatment of urinary diseases (e.g., neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis), or respiratory diseases (e.g., chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis).

Hereinafter, the compound (I) of the present invention will be described in detail.

Different from the conventional muscarinic M_3 receptor antagonist, the compound (I) of the present invention is structurally characterized in that it has as a basic skeleton a tetrahydroisoquinoline skeleton (Ia) or isoindoline skeleton (Ib) having a quinuclidinyloxycarbonyl group, etc. bonded to the nitrogen atom in the ring as shown below.



Furthermore, the compound (I) of the present invention is characterized in that it has ring A, that is, a cyclic group selected from an aryl group, a cycloalkyl group, a cycloalkenyl group, a heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, at the 1-position of the tetrahydroisoquinoline or isoindoline through X.

Unless otherwise specified, the term "lower" as used in the definition of the general formula in this specification means a linear or branched carbon chain having 1 to 6 carbon atoms. Accordingly, the "lower alkyl group" means linear or branched alkyl group having 1 to 6 carbon atoms. Specific examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl,

1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl groups. Among these groups, alkyl groups having 1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl and butyl groups are preferred, and a methyl group is more preferred.

The "aryl group" means aromatic hydrocarbon groups and preferably aryl groups having 6 to 14 carbon atoms. Specific examples include phenyl, naphthyl, indenyl, anthryl and phenanthryl groups, and a phenyl group is more preferred.

Examples of the "cycloalkyl group" include those having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Among these groups, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups are preferred, and a cyclohexyl group is more preferred.

Examples of the "cycloalkenyl group" include those having 3 to 8 carbon atoms such as 1-cyclopropenyl, 2-cyclopropenyl, 1-cyclobutenyl, 2-cyclobutenyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cyloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, 4-cycloheptenyl, 1-cyclooctenyl, 2-cyclooctenyl, 3-cyclooctenyl, 4-cyclooctenyl, 2,4-cyclopentadienyl,

2,5-cyclohexadienyl, 2,4-cycloheptadienyl, and 2,6-cycloheptadienyl.

The "heteroaryl group containing 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom" means a 5- or 6-membered heteroaryl group which may be condensed with a benzene ring. Specific examples include 5- or 6-membered monocyclic heteroaryl groups containing 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, such as furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl groups; and 5- or 6-membered heteroaryl groups condensed with a benzene ring, such as indolyl, indazolyl, indolizinyl, quinolyl, quinazolinyl, quinolizinyl, quinoxalinyl, cinnolinyl, benzimidazolyl, benzofuranyl, dihydrobenzofuranyl, benzoisoxazolyl, benzooxazolyl, benzothiazolyl and benzothienyl groups.

Among these groups, preferred are 5- or 6-membered monocyclic heteroaryl groups containing 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, and furyl, thienyl and pyridyl groups are more preferred.

The "5- to 7-membered saturated heterocyclic group" means a 5-, 6- or 7-membered saturated heterocyclic group containing 1 to 2 oxygen, nitrogen and/or sulfur atoms.

Specific examples include pyrrolidinyl, imidazolydinyl, piperidinyl, piperazinyl and morpholinyl groups.

The "aryl group", "cycloalkyl group", "cycloalkenyl group", "heteroaryl group containing 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom", "5- or 6-membered monocyclic heteroaryl group containing 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom", or "5- to 7-membered saturated heterocyclic group" as the group A may be substituted by an optional substituent. The number of the substituent is not limited to one but may be plural. Any group that can substitute for such a ring can be employed as the optional substituent. Preferred examples include a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group and a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxyl group, an amino group or a mono- or di-lower alkylamino group; a

halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group, a nitro group, a cyano group, an amino group and a mono- or di-lower alkylamino group are more preferred; a halogen atom, a lower alkyl group, a hydroxyl group and a lower alkoxy group are still more preferred; and a halogen atom and a lower alkyl group are particularly preferred.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine. When the substituent is a halogen atom, the number of the substituents is not particularly limited. When two or more halogen atoms are substituted, any combination of the above atoms is possible. Examples of the halogen atom-substituted lower alkyl group include fluoromethyl, chloromethyl, bromomethyl, iodomethyl, 1-fluoroethyl, 1-chloroethyl, 1-bromoethyl, 2-chloroethyl, 2-bromoethyl, dichloromethyl, trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl and dichlorobromomethyl. Among these groups, a trifluoromethyl group is preferred.

Examples of the "lower alkoxy group" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy (amyloxy), isopentyloxy, tert-pentyloxy, neopentyloxy, 2-methylbutoxy, 1,2-dimethylpropoxy, 1-ethylpropoxy and hexyloxy. Among these groups, lower alkoxy groups containing an alkyl group having 1 to 4 carbon atoms, such as methoxy, ethoxy, propoxy and butoxy are preferred, and methoxy and ethoxy groups are more preferred.

Examples of the lower alkoxycarbonyl group include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxy(amyloxy)carbonyl, isopentyloxycarbonyl, tert-pentyloxycarbonyl, neopentyloxycarbonyl, 2-methylbutoxycarbonyl, 1,2-dimethylpropoxycarbonyl, 1-ethylpropoxycarbonyl and hexyloxycarbonyl.

Examples of the "lower acyl group" include formyl, acetyl, propionyl, butyryl, valeryl and pivaloyl, and formyl, acetyl and propionyl are preferred.

The "lower alkylthio group" means a mercapto group of which hydrogen atom has been substituted by the above-exemplified lower alkyl group, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, pentylthio and hexylthio groups.

Examples of the "lower alkylsulfonyl group" include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, pentylsulfonyl and hexylsulfonyl.

Examples of the "lower alkylsulfinyl group" include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl and hexylsulfinyl.

Examples of the "lower alkanesulfonamido group" include methanesulfonamido, ethanesulfonamido,

propanesulfonamido, isopropanesulfonamido, butanesulfonamido, pentanesulfonamido and hexanesulfonamido.

The "mono- or di-lower alkylcarbamoyl group" means a carbamoyl group in which one or two hydrogen atom(s) have been substituted by the above-exemplified lower alkyl group(s), such as methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl and dimethylcarbamoyl groups.

The "mono- or di-lower alkylamino group" means an amino group in which one or two hydrogen atom(s) have been substituted by the above-exemplified lower alkyl group(s), such as methylamino, ethylamino, propylamino, dimethylamino, diethylamino and dipropylamino groups.

The term "lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group" means a lower alkyl group in which at least one optional hydrogen atom has been substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group. The lower alkyl group substituted by a halogen atom is as described in the above description of the halogen atom.

The compound (I) of the present invention contains a quinuclidinyl group. The nitrogen atom of the quinuclidinyl group may form oxide (ℓ = 1) or quaternary ammonium salt. Where a quaternary ammonium salt is formed, specific examples

of the group bound to the nitrogen atom include lower alkyl, lower alkenyl and lower alkynyl.

The term "lower alkenyl" as used herein means a linear or branched alkenyl group having 2 to 6 carbon atoms, such as vinyl, propenyl, butenyl, methylpropenyl, dimethylvinyl, pentenyl, methylbutenyl, dimethylpropenyl, ethylpropenyl, hexenyl, dimethylbutenyl and methylpentenyl. Among these groups, a propenyl group is preferred.

The "lower alkynyl group" means a linear or branched alkynyl group having 2 to 6 carbon atoms, such as ethynyl, propynyl, butynyl, methylpropynyl, pentynyl, methylbutynyl and hexynyl groups. Among these groups, alkynyl groups having 2 to 3 carbon atoms such as ethynyl and propynyl are preferred.

The anion for the quaternary ammonium salt is not particularly limited and the examples include ions of a halogen atom, triflate, tosylate and mesylate, preferably ions of a halogen atom, i.e. halide ions (e.g., chloride ion, bromide ion, iodide ion and triiodide ion). Examples of other anions include inorganic anions such as nitrate ion, sulfate ion, phosphate ion and carbonate ion, carboxylates such as formate ($HCOO^-$), acetate (CH_3COO^-), propionate, oxalate and malonate, and amino acid anions such as glutamate. Among the halide ions, bromide ion and iodide ion are preferred. Incidentally, the anion can be converted into

a preferable anion as needed by the ordinary ion exchange reaction.

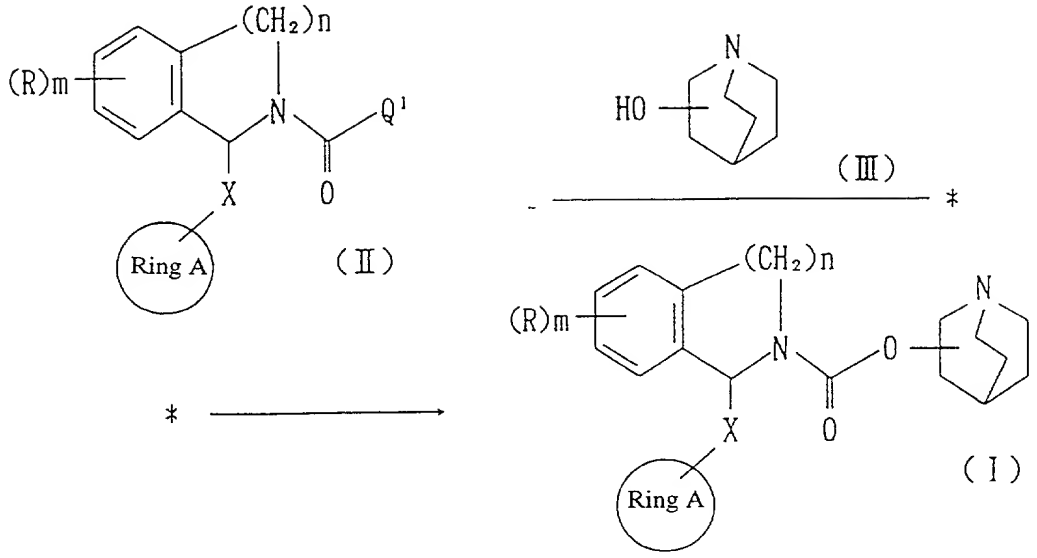
The compound (I) of the present invention contains an asymmetric carbon atom so that there exist optical isomers based on it. In addition, some of the invention compounds have stereoisomers or tautomers. The present invention also embraces diastereomers and enantiomers obtained by the separation of the above isomers as well as mixtures thereof.

Some of the compounds (I) of the present invention can form salts with an acid as well as the above-described quaternary ammonium salts with a quinuclidynyl group. Examples of such salt include acid addition salts with a mineral acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid or phosphoric acid; and those with an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, citric acid, tartaric acid, carbonic acid, picric acid, methanesulfonic acid, ethanesulfonic acid or glutamic acid. The compounds (I) of the present invention also embrace hydrates, solvates with ethanol or the like, and substances in any polymorphism crystals.

(Preparation Process)

The compound (I) of the present invention can be prepared in accordance with various processes. The typical preparation processes are explained below.

First preparation method



(in the formula, Q^1 represents a leaving group which is advantageous in the present reaction, and ring A, R, X, m and n have the same meanings as defined above. Hereinafter, the same will apply similarly).

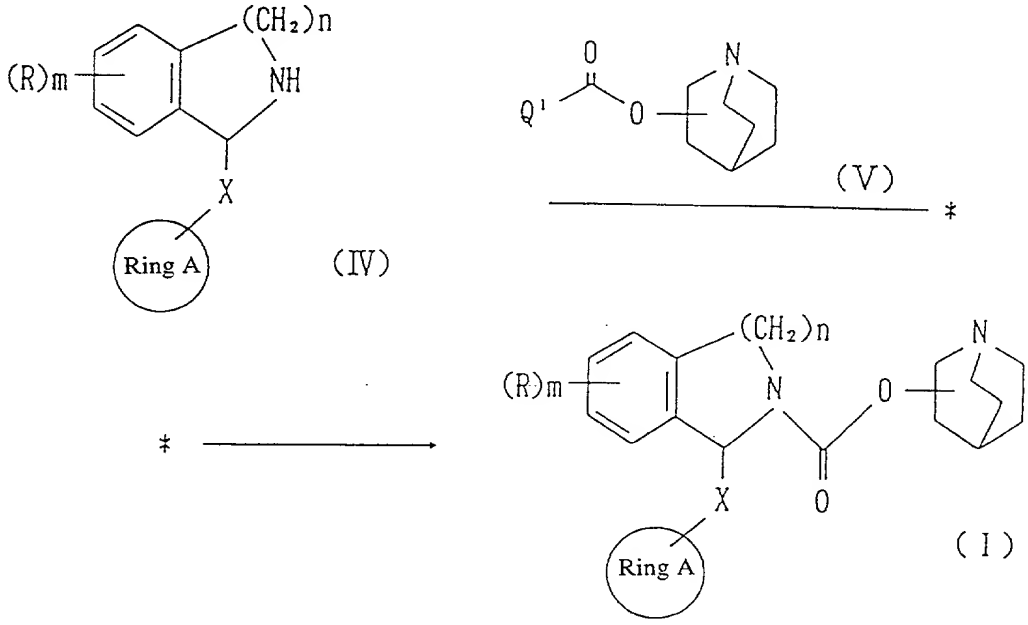
This reaction is carried out by stirring the compound represented by the general formula (II) and quinuclidinol represented by the general formula (III) in an amount corresponding to the reaction in an inert solvent at room temperature or under heating.

The leaving group Q^1 embraces, for example, a halogen atom, a lower alkoxy group, a phenoxy group and an imidazolyl group.

Examples of the inert solvent include dimethylformamide (DMF), dimethylacetamide, tetrahydrofuran (THF), dioxane, dimethoxyethane, diethoxyethane, benzene, toluene and xylene and mixed solvents thereof.

It is preferable to add a base (e.g., sodium, sodium hydride, sodium methoxide and sodium ethoxide) in order to accelerate the present reaction.

Second preparation method



(wherein the ring A, R, X, m, n and Q^1 have the same meanings as defined above.)

This reaction is carried out by stirring the compound represented by the general formula (IV) and the compound represented by the general formula (V) in the above-described inert solvent at room temperature or under heating.

It is preferable to add a base (e.g., sodium, sodium hydride, sodium methoxide, sodium ethoxide, triethylamine and pyridine) in order to accelerate the present reaction.

(Other preparation methods)

Among the compounds of the present invention, a compound in which the nitrogen atom of the quinuclidinyl group forms oxide or a quaternary ammonium salt can be prepared by N-oxide formation or N-alkylation of a tertiary amine compound in the compounds of the present invention.

The N-oxide formation reaction can be carried out by the oxidation reaction in a conventional manner, more specifically, by stirring a tertiary amine compound in the compounds of the present invention and a corresponding amount or excess amount of oxidizing agent in an inert solvent such as chloroform, dichloromethane or dichloroethane, an alcohol such as methanol or ethanol or water or a mixed solvent thereof under cooling or at room temperature, or in some cases under heating. Examples of the oxidizing agent include organic peracids such as m-chloroperbenzoic acid, sodium periodate and hydrogen peroxide.

The N-alkylation reaction can be carried out in accordance with the conventional N-alkylation reaction, more

specifically by stirring a tertiary amine compound in the compound of the present invention and a corresponding amount of an alkylating agent in an inert solvent such as dimethylformamide, chloroform, benzene, 2-butanone, acetone or tetrahydrofuran under cooling or a room temperature, or in some cases under heating.

Examples of the alkylating agent include lower alkyl halides, lower alkyl trifluoromethanesulfonates, lower alkyl p-toluenesulfonates and lower alkyl methanesulfonates, preferably lower alkyl halides.

For the preparation of the compound of the present invention, it is sometimes necessary to protect a functional group. In such a case, introduction of a proper protecting group and deprotection operation in a conventional manner are carried out additionally.

The compound of the present invention so prepared is provided as is in the free form, or after subjected to the salt formation treatment in a conventional manner, it is isolated and purified as its salt. Isolation and purification are carried out by the ordinary chemical operation such as extraction, concentration, evaporation, crystallization, filtration, recrystallization or a variety of chromatography.

Industrial Applicability

The compound of the present invention has affinity and selectivity for the muscarinic M_3 receptor and, as an M_3 receptor antagonist, it is useful as an agent for prevention or treatment of various M_3 receptor-related diseases, particularly urinary diseases such as urinary incontinence or pollakiuria in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm or chronic cystitis; respiratory diseases such as chronic obstructive pulmonary diseases, chronic bronchitis, asthma or rhinitis; or digestive diseases such as irritable bowel syndrome, spastic colitis or diverticulitis.

In particular, the compound of the present invention has high selectivity for the M_3 receptor existing in the smooth muscle or gland tissues compared with the M_2 receptor existing in the heart or the like, so that it has high utility as an M_3 receptor antagonist having less side effects on the heart or the like, particularly as an agent for prevention or treatment of urinary incontinence, pollakiuria, chronic obstructive pulmonary diseases, chronic bronchitis, asthma or rhinitis.

The affinity and antagonism of the compound of the present invention for the muscarinic receptor was confirmed by the following tests.

Muscarinic receptor affinity test (*in vitro*)

a. Preparation of membranes

From a male Wistar rat (Japan SLC), the heart and submandibular gland were excised, mixed with a 20 mM HEPES buffer (pH 7.5, which will hereinafter be abbreviated as "HEPES buffer") containing 5 times the volume of 100 mM sodium chloride and 10 mM magnesium chloride was added, followed by homogenization under ice-cooling. The resulting mixture was filtered through gauze, followed by ultracentrifugation at 50,000 × g and 4°C for 10 minutes. The precipitate obtained was suspended in an HEPES buffer, followed by further ultracentrifugation at 50,000 × g and 4°C for 10 minutes. The precipitate obtained was suspended in an HEPES buffer. The resulting suspension was stored at -80°C and provided for the test after melting upon use.

b. Muscarinic M_2 receptor binding test

The test was carried out in accordance with the method of Doods et al. (*J. Pharmacol. Exp. Ther.*, 242, 257-262, 1987) with some modifications. The cardiac membrane sample, [^{3}H]-quinuclidinyl benzilate and the test compound were incubated in a 0.5 ml HEPES buffer at 25°C for 45 minutes, followed by suction filtration through a glass filter (Whatman GF/B). The filter was washed three times with 5 ml portions of an HEPES buffer. The radioactivity of the [^{3}H]-quinuclidinyl benzilate adsorbed on the filter was measured by a liquid scintillation counter. Incidentally,

nonspecific binding of the receptor was determined by the addition of 1 μM atropine. The affinity of the compound of the present invention for the muscarinic M_2 receptor was determined from a dissociation constant (Ki) calculated, in accordance with Chen and Prusoff (*Biochem. Pharmacol.* 22, 3099, 1973), based on the concentration (IC_{50}) of the test compound at which 50% of the binding of the [^{3}H]-quinuclidinyl benzilate, that is, a labeled ligand was inhibited.

c. Muscarinic M_3 receptor binding test

In a similar manner to the above muscarinic M_2 receptor binding test except that the submandibular gland was used as a membrane sample and [^{3}H]-N-methylscopolamine was used as a labeled ligand, a muscarinic M_3 receptor binding test was carried out.

Results: The compound (I) of the present invention had a Ki value of from 10^{-8} to 10^{-10} for M_3 receptor, which suggested that the affinity for M_3 receptor was at least 10 times as high as that for M_2 receptor.

Muscarinic receptor antagonism test (*in vivo*)

a. Test on rhythmic bladder contraction in rat

A female Wistar rat (130-200 g) was subjected to urethane anesthesia (1.0 g/kg s.c.), followed by ligation of the ureter on the kidney side. A urethral catheter was allowed to remain in the bladder, and about 1.0 ml of physiological saline was injected into the bladder through

the catheter to cause rhythmic bladder contraction. Intravesical pressure was measured by a pressure transducer. After rhythmic contraction continued stable for at least 5 minutes, the test compound was cumulatively administered from the external jugular vein. Five to ten minutes later, the intravesical pressure was measured. An inhibition ratio of bladder contraction was determined compared with the bladder contraction before administration of the test compound and the dose of the test compound required for 30% inhibition of the bladder contraction before administration was designated as ED_{30}.

As a result of the test, the compound of the present invention showed good ED_{30} value.

b. Test on salivary secretion in rat

A male Wistar rat (160-190 g) was subjected to anesthesia with urethane (0.8 g/kg i.p.), and the test compound was administered (to the control group: solvent). Fifteen minutes later, 0.8 μmol/kg of oxotremorine was administered. In each case, the drug was administered through its femoral artery. The saliva secreted for 5 minutes after the administration of oxotremorine was collected and weighed. The inhibition ratio against the amount of saliva in the control group was determined and the dose of the test compound required for 50% inhibition of the amount of saliva in the control group was designated as ID_{50}.

As a result of the test, the ID_{50} value of atropine tested as a comparative compound was substantially the same with the ED_{30} value obtained in the above rat rhythmical bladder contraction test, while the ID_{50} value of the invention compound was at least 5 times as much as the above-described ED_{30} value, which suggested that the compound of the present invention has relatively weak action against the salivary secretion.

c. Test on bradycardia in rat

The test was carried out in accordance with the method of Doods et al. (*J. Pharmacol. Exp. Ther.*, 242, 257-262, 1987). A male Wistar rat (250-350 g) was subjected to anesthesia with pentobarbital sodium (50 mg/kg i.p.). The neck region was excised, followed by the division of right and left vagus nerves. After a cannula was inserted into a trachea to secure airway, a stainless rod was inserted from the orbit and the spinal cord was destroyed. Under artificial respiration (at 10 cc/kg and 50 times/minute), the rectal temperature was maintained at 37.5°C and a heart rate was monitored at the common carotid artery. An indwelling needle was fixed to the femoral artery, from which the drug was administered. After the destruction of the spinal cord, the rat was allowed to stand for 15 minutes to attain the equilibrium, followed by the administration of atenolol (10 mg/kg). After the equilibration for additional 15 minutes, the test compound was administered. Fifteen minutes

later, oxotremorine was cumulatively administered, thereby the reduction in the heart rate was measured. The amount of the test compound required for 10-times rightward shift of the dose-response curve of the control group was designated as DR_{10}.

Results: The compound (I) of the present invention had sufficiently low activity against bradycardia and no bradycardia was observed at the administration amount of several mg/kg.

As a result of the above-described muscarinic receptor affinity test (*in vitro*), it was found that the compound (I) of the present invention had selectivity and high affinity for M_3 receptor. Even in the muscarinic receptor antagonism test (*in vivo*), the compound of the present invention showed good muscarinic M_3 antagonistic activity but low activity on the bradycardia having relationship with muscarinic M_2 receptor. Accordingly, it was found that the compound (I) of the present invention has selective antagonistic activity against muscarinic M_3 receptor, and furthermore, it has less side effects such as dry mouth compared with the conventional anti-cholinergic agent.

A pharmaceutical composition containing one or more of the compounds of the present invention and salts thereof is prepared using an ordinary pharmaceutically acceptable carrier.

In the present invention, the administration of the pharmaceutical composition can be carried out either orally or parenterally in the form of an injection, suppository, transdermal agent, inhalant or intravesical injection.

The dose is optionally determined in each case in consideration of the conditions, age, sex and the like of the patient to be administered. In the oral administration, the daily dose may generally range from about 0.01 mg/kg to 100 mg/kg per adult. It is administered once or in 2-4 portions. Where intravenous administration is adopted in consideration of the conditions of the patient, the daily dose may generally range from about 0.001 mg/kg to 10 mg/kg per adult, once or plural portions per day.

Examples of the pharmaceutical carrier include nontoxic solid or liquid pharmaceutical substances.

Examples of the solid composition for the oral administration include tablets, pills, capsules, powders and granules, or the like. In such solid compositions, one or more active substances are mixed with at least one inert diluent such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, agar, pectin, magnesium metasilicate or magnesium aluminate. In the composition, it is possible to incorporate additives other than the above inert diluent, for example, a lubricant such as magnesium stearate, a disintegrator such as cellulose calcium glycolate, a

stabilizer such as lactose, a solubilization aid such as glutamic acid or aspartic acid in a conventional manner. A tablet or pill may optionally be coated with sugar or a film of a gastric or enteric substance such as sucrose, gelatin, hydroxypropylcellulose or hydroxypropylmethylcellulose phthalate.

Examples of the liquid composition for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs which contain a commonly employed inert diluent such as purified water or ethanol. The composition can also contain, in addition to such an inert diluent, a wetting agent, auxiliary agent such as suspending agent, sweetener, flavoring agent, aroma and/or antiseptic.

The injection for parenteral administration according to the present invention include a sterile aqueous or nonaqueous solution, suspension or emulsion. Examples of the aqueous solution and suspension include distilled water and physiological saline for injection. Examples of the non-water-soluble solution or suspension include ethylene glycol, polypropylene glycol, polyethylene glycol, vegetable oils such as cacao butter, olive oil or sesame oil, alcohols such as ethanol, gum arabic and "Polysolvate 80" (trade name). Such a composition may further contain an isotonicity agent, antiseptic agent, wetting agent, emulsifying agent, dispersing agent, stabilizer (for example, lactose) and/or

solubilizing aid (for example, glutamic acid, aspartic acid). They are sterilized by, for example, filtration through a bacteria-retaining filter, incorporation of a sterilizer, or irradiation. Alternatively, a sterile solid composition which has been prepared in advance is dissolved in sterile water or a sterile injection solvent upon use.

Best Modes for Carrying out the Invention

The present invention will hereinafter be described in further detail with reference to the following Examples. However, the compounds of the present invention should not be construed as being limited to the compounds which will be described later in Examples but embrace all the compounds represented by the above formula (I) and salts, hydrates, solvates, geometrical and optical isomers and any polymorphism forms of the compound (I).

Incidentally, the starting compounds for the compound of the present invention include novel compounds and preparation examples of such starting compounds will be described below as Reference Examples.

Reference Example 1

To a 130 ml dichloromethane solution containing 6.28 g of 1-phenyl-1,2,3,4-tetrahydroisoquinoline and 3.34 g of triethylamine, 3.1 ml of ethyl chloroformate was added dropwise under ice-cooling, followed by stirring at room temperature overnight. The reaction solution was washed

successively with water, 1N hydrochloric acid, water and brine and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, thereby 10.58 g of ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate was obtained as pale yellow oil.

Infrared absorption spectrum νmax(neat)cm^{-1}: 1700, 1430, 1296, 1230, 1122.

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS internal standard)

δ: 1.29 (3H, t, J = 7.3 Hz), 2.75-3.45 (3H, m), 3.90-4.40 (1H, m), 4.21 (2H, q, J = 7.3 Hz), 6.38 (1H, s), 6.95-7.45 (9H, m).

In a similar manner to Reference Example 1, the compounds of the following Reference Examples 2 to 14 were obtained.

Reference Example 2

Methyl 1-phenyl-2-isoindolinecarboxylate

Starting compounds: 1-phenylisoindoline, methyl chloroformate

Infrared absorption spectrum νmax(KBr)cm^{-1}: 1708, 1460, 1376, 1100

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS internal standard)

δ: 3.60, 3.72 (3H, s × 2), 4.89, 4.96 (2H, s × 2), 5.94, 6.03 (1H, s × 2), 6.95-7.10 (1H, m), 7.15-7.35 (8H, m)

Reference Example 3

Ethyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-(4-pyridyl)-1,2,3,4-tetrahydroisoquinoline

Properties: pale yellow oil

Mass analysis (m/z, EI): 282 (M^+)

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS internal standard)

δ: 1.29 (3H, t, J = 7.1 Hz), 2.60-3.45 (3H, m), 3.85-4.20 (1H, m), 4.22 (2H, q, J = 7.1 Hz), 6.31 (1H, s), 7.14 (2H, dd, J = 4.4, 1.5 Hz), 7.17-7.26 (4H, m), 8.51 (2H, dd, J = 4.4, 1.5 Hz)

Reference Example 4

Ethyl 1,2,3,4-tetrahydro-1-(2-thienyl)-2-isoquinolinecarboxylate

Starting compound: 1,2,3,4-tetrahydro-1-(2-thienyl)isoquinoline

Properties: pale yellow oil

Mass analysis (m/z, EI): 287 (M^+)

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS internal standard)

δ: 1.32 (3H, t, J = 7.3 Hz), 2.65-3.60 (3H, m), 4.00-4.30 (1H, m), 4.23 (2H, q, J = 7.3 Hz), 6.53 (1H, s), 6.70-6.95 (2H, m), 7.15-7.30 (5H, m)

Reference Example 5

Ethyl 1,2,3,4-tetrahydro-1-(3-thienyl)-2-isoquinolinecarboxylate

Starting compound: 1,2,3,4-tetrahydro-1-(3-thienyl)-isoquinoline

Properties: Orange oil

Mass analysis (m/z, FAB): 288 ($M^+ + 1$)

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS internal standard)

δ: 1.2-1.3 (3H, m), 2.7-2.8 (1H, m), 2.9-3.0 (1H, m), 3.1-3.3 (1H, m), 3.9-4.2 (3H, m), 6.2-6.4 (1H, m), 6.83 (1H, s), 6.95-7.26 (6H, m)

Reference Example 6

Ethyl 1-(2-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-(2-furyl)-1,2,3,4-tetrahydroisoquinoline

Mass analysis (m/z, EI): 271 (M^+)

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS internal standard)

δ: 1.30 (3H, t, J = 6.5 Hz), 2.75-2.85 (1H, m), 2.90-3.10 (1H, m), 3.20-3.50 (1H, m), 4.05-4.35 (4H, m), 6.00 (1H, s), 6.20-6.45 (2H, m), 7.15-7.25 (4H, m), 7.33 (1H, s)

Reference Example 7

(1R)-Ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline

Elemental analysis (for $C_{18}H_{19}NO_2$)

	C (%)	H (%)	N (%)
Calcd.:	76.84	6.81	4.98
Found:	76.53	6.82	4.93

Specific optical rotation $[\alpha]_D^{25}$: 199.2 (C = 1.03, $CHCl_3$)

Mass analysis (m/z, FAB): 282 ($M^+ + 1$)

Reference Example 8

(1S)-Ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: (1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline

Elemental analysis (for $C_{18}H_{19}NO_2$)

	C (%)	H (%)	N (%)
Calcd.:	76.84	6.81	4.98
Found:	76.64	6.82	4.99

Specific optical rotation $[\alpha]_D^{25}$: -200.9 (C = 1.09, $CHCl_3$)

Mass analysis (m/z, EI): 281 (M^+)

Reference Example 9

Ethyl 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline

Properties: Pale yellow oil

Mass analysis (m/z, EI): 315 (M^+)

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS Internal standard)

δ: 1.29 (3H, t, J = 7.0 Hz), 2.70-3.52 (3H, m), 4.00-4.30 (1H, m), 4.20 (2H, q. J = 7.0 Hz), 6.35 (1H, s), 7.05-7.35 (8H, m)

Reference Example 10

Ethyl 1-(4-fluorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline

Properties: Pale yellow oil

Mass analysis (m/z, FAB): 300 ($M^+ + 1$)

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS internal standard)

δ: 1.30 (3H, t, J = 8.9 Hz), 2.75 (1H, dd, J = 12.5, 3.4 Hz), 2.9-3.1 (1H, m), 3.1-3.3 (1H, m), 4.0-4.3 (3H, m), 6.2-6.4 (1H, m), 6.93-7.03 (3H, m), 7.16-7.24 (5H, m).

Reference Example 11

Ethyl 1,2,3,4-tetrahydro-1-(4-tolyl)-2-isoquinolinecarboxylate

Starting compound: 1,2,3,4-tetrahydro-1-(4-tolyl)isoquinoline

Mass analysis (m/z, EI): 295 (M^+)

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS internal standard)

δ: 1.20-1.35 (3H, m), 2.30 (3H, s), 2.70-2.80 (1H, m), 2.90-3.10 (1H, m), 3.23 (1H, t, J = 10.0 Hz), 3.95-4.30 (3H, m), 6.29, 6.41 (1H, brs × 2), 7.00-7.25 (8H, m).

Reference Example 12

Ethyl 1-benzyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-benzyl-1,2,3,4-tetrahydroisoquinoline

Properties: Pale yellow oil

Mass analysis (m/z, FAB): 296 ($M^+ + 1$)

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS internal standard)

δ: 1.02, 1.23 (3H, t × 2, J = 7.1 Hz), 2.63-3.20 (4H, m), 3.30-3.50 (1H, m), 3.75-4.25 (3H, m), 5.27, 5.38 (1H, t × 2, J = 6.8 Hz), 6.85-7.28 (9H, m).

Reference Example 13

Ethyl 1-cyclohexyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-cyclohexyl-1,2,3,4-tetrahydroisoquinoline

Properties: yellow oil

Mass analysis (m/z, FAB): 288 ($M^+ + 1$)

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS internal standard)

δ: 0.70-2.00 (11H, m), 1.26 (3H, t, J = 7.3 Hz), 2.89 (2H, t, J = 7.1 Hz), 3.25-4.20 (2H, m), 4.14 (2H, q, J = 7.1 Hz), 4.65-4.95 (1H, m), 7.00-7.30 (4H, m).

Reference Example 14

Ethyl 1-(3-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-(3-furyl)-1,2,3,4-tetrahydroisoquinoline

Properties: yellow oil

Mass analysis (m/z, EI): 271 (M^+)

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS internal standard)

δ: 1.31 (3H, t, J = 7.0 Hz), 2.55-3.40 (3H, m), 3.90-4.30 (1H, m), 4.22 (2H, q, J = 7.0 Hz), 6.20-6.45 (2H, m), 6.95-7.40 (6H, m).

The chemical structural formulas of the compounds obtained in Reference Examples 1-14 are shown in the following Tables 1-2.

Table 1

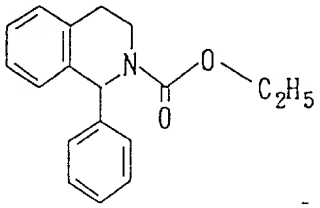
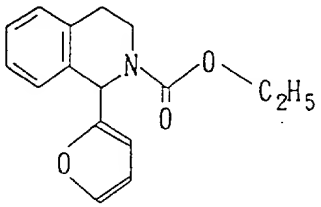
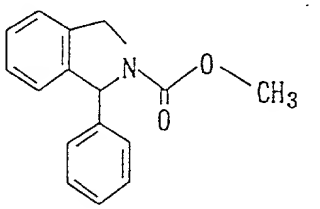
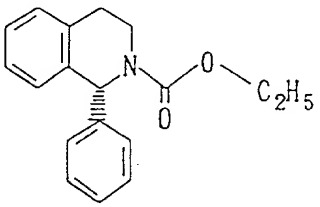
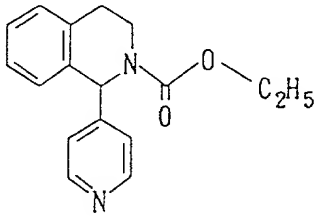
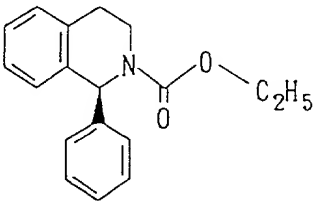
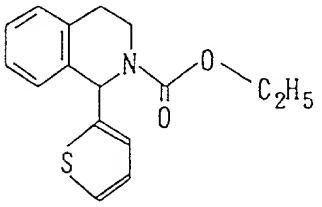
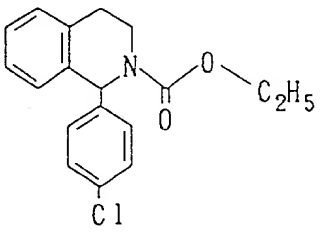
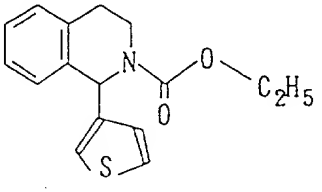
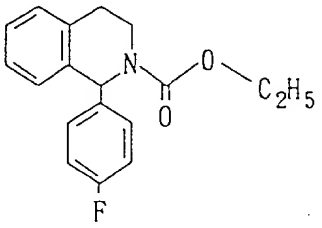
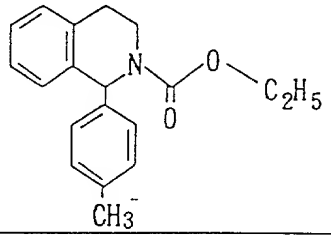
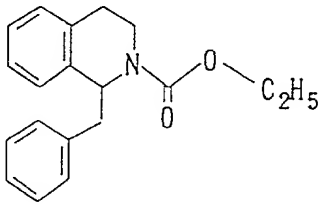
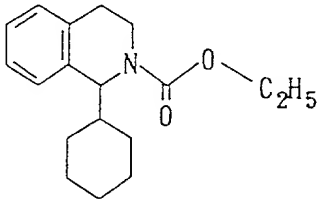
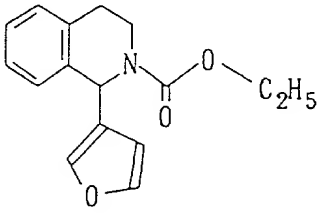
Reference Example No.	Structural Formula	Reference Example No.	Structural Formula
1		6	
2		7	
3		8	
4		9	
5		10	

Table 2

Reference Example No.	Structural Formula
11	
12	
13	
14	

Example 1

To a 30 ml toluene solution containing 0.70 g of ethyl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate and 0.41 g of 3-quinuclidinol, 0.03 g of sodium hydride (60%) was added. The resulting mixture was stirred at 140°C for 2 days while removing the ethanol formed. The reaction mixture was cooled to room temperature, brine was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform : methanol = 10 : 1 → chloroform : methanol : 28% aqueous ammonia = 10 : 1 : 0.1), thereby 0.11 g of 3-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate was obtained as yellow oil. The resulting oil was dissolved in 10 ml of ethanol, followed by the addition of 27 mg of oxalic acid. Then, the solvent was removed under reduced pressure. The resulting solid was recrystallized from isopropanol and isopropyl ether, thereby 0.08 g of 3-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monooxalate was obtained as colorless crystals.

Melting point: 122-124°C (i-PrOH-i-Pr_2O)

Elemental analysis (for $C_{25}H_{28}N_2O_6 \cdot 0.75H_2O$)

	C (%)	H (%)	N (%)
Calcd.:	64.43	6.38	6.01
Found:	64.25	6.15	5.88

In a similar manner to Example 1, the compound of Example 2 was obtained.

Example 2

3-Quinuclidinyl 1-phenyl-2-isoindolinecarboxylate monohydrochloride

Starting compound: methyl 1-phenyl-2-isoindolinecarboxylate

Melting point: 164-165°C (EtOH-Et_2O)

Elemental analysis (for $C_{22}H_{25}N_2O_2Cl \cdot 1.75H_2O$)

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	63.45	6.90	6.73	8.51
Found:	63.54	6.59	6.76	8.12

Example 3

To a 50 ml toluene suspension containing 720 mg of ethyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate and 973 mg of 3-quinuclidinol, 102 mg of sodium hydride (60%) was added at room temperature. The resulting mixture was heated under reflux for 5 hours and 40 minutes while the resulting ethanol was removed together with toluene. The reaction mixture was cooled to room temperature, followed by addition of 20 ml of water. The resulting mixture was extracted with chloroform. The organic layer was washed with water and brine, dried over anhydrous

sodium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform : methanol : 28% aqueous ammonia = 100 : 2 : 1), thereby 827 mg of 3-quinuclidinyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate were obtained as yellow oil. The resulting oil was dissolved in 5 ml of ethyl acetate, 2 ml of a 4N hydrogen chloride in ethyl acetate solution was added. The solvent was then removed under reduced pressure. Ethanol and ether were added to the residue, and the crude crystals thus obtained was recrystallized from ethanol and ether, thereby 402 mg of 3-quinuclidinyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate dihydrochloride was obtained as pale yellow crystals.

Melting point: 167-169°C (EtOH-Et_2O)

Elemental analysis (for $C_{22}H_{27}N_3O_2Cl_2 \cdot 2.2H_2O$)

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	55.51	6.65	8.83	14.90
Found:	55.46	6.98	8.64	14.84

In a similar manner to Example 3, the compounds of Examples 4 to 6 which will be described below were obtained.

Example 4

3-Quinuclidinyl 1,2,3,4-tetrahydro-1-(2-thienyl)-2-isoquinolinecarboxylate monooxalate

Starting compound: Ethyl 1,2,3,4-tetrahydro-1-(2-thienyl)-2-isoquinolinecarboxylate

Elemental analysis (for $C_{23}H_{26}N_2O_6S \cdot 1.3H_2O$)

	C (%)	H (%)	N (%)	S (%)
Calcd.:	57.32	5.98	5.81	6.65
Found:	57.62	6.00	5.84	6.27

Mass analysis (m/z, FAB): 369 ($M^+ + 1$)

Example 5

(1RS,3'R)-3'-Quinuclidinyl 1,2,3,4-tetrahydro-1-(3-thienyl)-2-isoquinolinecarboxylate

Starting compounds: ethyl 1,2,3,4-tetrahydro-1-(3-thienyl)-2-isoquinolinecarboxylate, (3R)-3-quinuclidinol

Properties: Brown oil

Elemental analysis (for $C_{21}H_{24}N_2O_2S \cdot 0.3H_2O$)

	C (%)	H (%)	N (%)	S (%)
Calcd.:	67.46	6.63	7.49	8.58
Found:	67.35	6.76	7.21	8.46

Mass analysis (m/z, FAB): 369 ($M^+ + 1$)

Example 6

3-Quinuclidinyl 1-(2-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: ethyl 1-(2-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Properties: Pale yellow oil

Elemental analysis (for $C_{21}H_{24}N_2O_3 \cdot 0.5H_2O$)

	C (%)	H (%)	N (%)
Calcd.:	69.79	6.97	7.75
Found:	70.03	7.05	7.44

Mass analysis (m/z, FAB): 353 ($M^+ + 1$)

Example 7

To a 30 ml pyridine solution containing 2.09 g of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, 2.26 g of 3-quinuclidinyl chloroformate monohydrochloride was added at room temperature, followed by stirring at 80°C for 4 hours. Then, 0.12 g of 3-quinuclidinyl chloroformate monohydrochloride, followed by stirring at 80°C for 4 hours. Then, 1.01 g of 3-quinuclidinyl chloroformate monohydrochloride was added, and the mixture was stirring at 80°C for 25 hours. The reaction mixture was concentrated under reduced pressure. Water was added to the residue, followed by washing with ethyl acetate twice. The resulting aqueous layer was adjusted to pH 9 with saturated sodium hydrogencarbonate aqueous solution, followed by extraction with ethyl acetate. After the organic layer was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, thereby 3.02 g of (1R,3'RS)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate was obtained as yellow oil.

Mass analysis (m/z, FAB): 363 ($M^+ + 1$)

Nuclear magnetic resonance spectrum (DMSO-d_6, TMS internal standard)

δ: 1.20-2.00 (5H, m), 2.40-2.95 (6H, m), 3.00-3.60 (3H, m), 3.80-3.95 (1H, m), 4.55-4.70 (1H, m), 6.25 (1H, brs), 7.05-7.35 (10H, m).

Example 8

To a 120 ml toluene suspension containing 12.0 g of (1R)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate and 16.27 g of (3R)-3-quinuclidinol, 1.69 g of sodium hydride (60%) was added at room temperature. The resulting mixture was heated for 3 hours while the resulting ethanol was removed together with toluene. The reaction mixture was cooled to room temperature, and 50 ml of brine was added, followed by extraction with ethyl acetate. The organic layer was washed with water and then extracted with 20% hydrochloric acid. The resulting aqueous layer was adjusted to pH 9 to 10 by adding a 1N aqueous solution of sodium hydroxide, followed by extraction with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was dissolved in 140 ml of ethanol, and 10 ml of a 4N hydrogen chloride in ethyl acetate solution was added to the resulting solution. The solvent was then removed under reduced pressure. Acetonitrile and ether were added to the residue, and the resulting crude crystals were recrystallized from acetonitrile and ether, thereby 10.1 g of (1R,3'R)-3'-

quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monohydrochloride was obtained as colorless crystals.

Melting point: 212-214°C (CH_3CN-Et_2O)

Elemental analysis (for $C_{23}H_{27}N_2O_2Cl$)

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	69.25	6.82	7.02	8.89
Found:	69.24	6.89	7.03	8.97

Specific optical rotation $[\alpha]_D^{25}$: 98.1 (C = 1.00, EtOH)

In a similar manner to Example 8, the compounds of the following Examples 9 to 16 were obtained.

Example 9

(1S,3'S)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monohydrochloride

Starting compounds: (1S)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, (3S)-3-quinuclidinol

Melting point: 211-212°C (EtOH-Et_2O)

Elemental analysis (for $C_{23}H_{27}N_2O_2Cl \cdot 0.25H_2O$)

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	68.48	6.87	6.94	8.79
Found:	68.32	6.75	6.94	8.94

Specific optical rotation $[\alpha]_D^{25}$: -97.4 (C = 0.50, EtOH)

Example 10

(1S,3'R)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monohydrochloride

Starting compounds: (1S)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, (3R)-3-quinuclidinol

Melting point: 195-196°C (EtOH-Et_2O)

Elemental analysis (for $C_{23}H_{27}N_2O_2Cl \cdot 0.25H_2O$)

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	68.48	6.87	6.94	8.79
Found:	68.73	6.88	6.95	8.70

Specific optical rotation $[\alpha]_D^{25}$: -151.2 (C = 0.50, EtOH)

Example 11

(1R,3'S)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monohydrochloride

Starting compounds: (1R)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, (3S)-3-quinuclidinol

Melting point: 194-195°C (CH_3CN-Et_2O)

Elemental analysis (for $C_{23}H_{27}N_2O_2Cl$)

	C (%)	H (%)	N (%)	Cl (%)
Calcd.:	69.25	6.82	7.02	8.89
Found:	69.08	6.71	6.99	8.91

Specific optical rotation $[\alpha]_D^{25}$: 163.2 (C = 0.50, EtOH)

Example 12

3-quinuclidinyl 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monofumarate

Starting compounds: 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Melting point: 164-166°C (EtOH-Et_2O)

Elemental analysis (for $C_{27}H_{29}N_2O_6Cl \cdot 0.5H_2O$)

	C (%)	H(%)	N(%)	Cl(%)
Calcd.:	62.13	5.79	5.37	6.79
Found:	62.19	5.68	5.23	6.49

Example 13

(1RS,3'R)-3'-quinuclidinyl 1-(4-fluorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compounds: ethyl 1-(4-fluorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, (3R)-3-quinuclidinol

Properties: colorless oil

Elemental analysis (for $C_{23}H_{25}N_2O_2F \cdot 0.1H_2O$)

	C (%)	H (%)	N (%)	F (%)
Calcd.:	72.27	6.64	7.33	4.97
Found:	72.05	6.63	7.15	4.99

Mass analysis (m/z, FAB): 381 ($M^+ + 1$)

Example 14

3-quinuclidinyl 1,2,3,4-tetrahydro-1-(4-tolyl)-2-isoquinolinecarboxylate

Starting compounds: ethyl 1,2,3,4-tetrahydro-1-(4-tolyl)-2-isoquinolinecarboxylate

Properties: colorless oil

Elemental analysis (for $C_{24}H_{28}N_2O_2 \cdot 0.8H_2O$)

	C (%)	H (%)	N (%)
Calcd.:	73.74	7.63	7.17
Found:	73.96	7.50	6.95

Mass analysis (m/z, FAB): 377 ($M^+ + 1$)

Example 15

3-Quinuclidinyl 1-benzyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: ethyl 1-benzyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Properties: pale yellow oil

Elemental analysis (for $C_{24}H_{28}N_2O_2 \cdot 0.5H_2O$)

	C (%)	H (%)	N (%)
Calcd.:	74.78	7.58	7.26
Found:	74.95	7.83	7.18

Mass analysis (m/z, FAB): 377 ($M^+ + 1$)

Example 16

3-Quinuclidinyl 1-cyclohexyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compounds: ethyl 1-cyclohexyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Properties: pale yellow amorphous

Elemental analysis (for $C_{23}H_{32}N_2O_2 \cdot 0.3H_2O$)

	C (%)	H (%)	N (%)
Calcd.:	73.88	8.79	7.49
Found:	73.76	8.75	7.37

Mass analysis (m/z, FAB): 369 ($M^+ + 1$)

Example 17

In 12 ml of dichloromethane, 1.20 g of (1R,3'R)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate was dissolved, 0.33 g of sodium

hydrogencarbonate and 0.79 g of m-chloroperbenzoic acid (80%) were added under ice-cooling, followed by stirring at room temperature for one hour. Water was added to the reaction mixture and then the mixture was extracted with dichloromethane. The organic layer was washed with an aqueous solution of sodium thiosulfate and then dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform : methanol = 20:1), thereby 0.43 g of (1'R,3R)-3-[[(1'-phenyl-1',2',3',4'-tetrahydro-2'-isoquinolyl)carbonyl]oxy]quinuclidine 1-oxide was obtained.

Properties: white amorphous

Mass analysis (m/z, FAB): 379 ($M^+ + 1$)

Nuclear magnetic resonance spectrum ($CDC\ell_3$, TMS internal standard)

δ: 1.85-2.15 (3H, m), 2.15-2.35 (2H, m), 2.75-2.90 (1H, m), 2.90-2.95 (1H, m), 3.20-3.50 (6H, m), 3.70-3.80 (1H, m), 3.85-4.10 (1H, m), 5.14 (1H, brs), 6.14, 6.43 (1H, brs × 2), 7.05-7.40 (9H, m).

Example 18

To a 8 ml 2-butanone solution containing 1.04 g of (1R,3'R)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 0.18 ml of methyl iodide was added, followed by stirring at 55°C for 40 minutes. After air cooling, the crystals precipitated were collected by

filtration and then washed successively with 2-butanone and diethyl ether, thereby 0.93 g of (1'R,3R)-1-methyl-3-[[(1'-phenyl-1',2',3',4'-tetrahydro-2'-isoquinolyl)carbonyl]oxy]quinuclidinium iodide was obtained as colorless crystals.

Melting point: 202-203°C (2-butanone)

Elemental analysis (for $C_{24}H_{29}N_2O_2I$)

	C (%)	H (%)	N (%)	I (%)
Calcd.:	57.15	5.79	5.55	25.16
Found:	57.17	5.71	5.51	25.15

In a similar manner to Example 8, the compound of the following Example 19 was obtained.

Example 19

(1RS,3'R)-3'-quinuclidinyl 1-(3-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: ethyl 1-(3-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Properties: yellow oil

Elemental analysis (for $C_{21}H_{24}N_2O_3 \cdot 0.3H_2O$)

	C (%)	H (%)	N (%)
Calcd.:	70.49	6.93	7.83
Found:	70.35	6.83	7.63

Mass analysis (m/z, EI): 352 (M^+)

The chemical structural formulas of the compounds obtained in Examples 1-19 are shown below in Tables 3-5.

Table 3

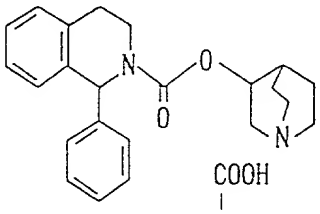
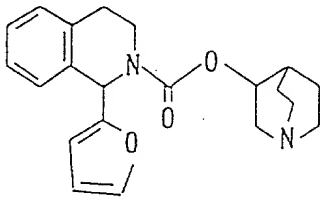
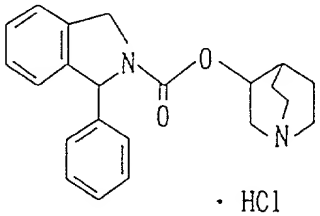
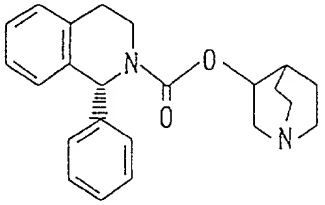
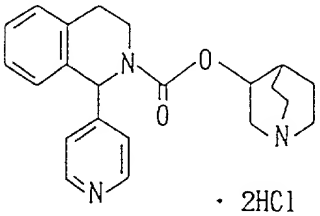
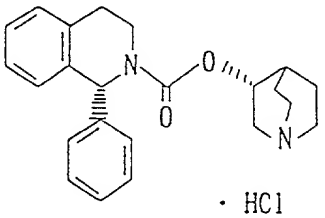
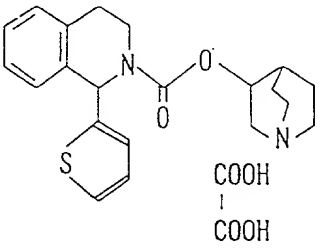
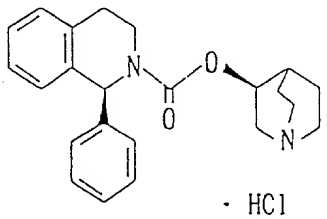
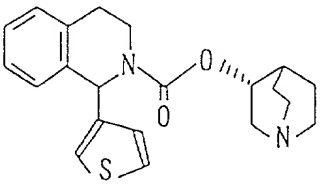
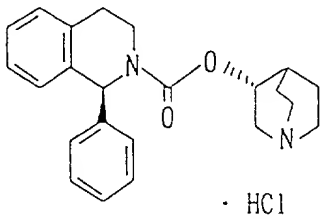
Example No.	Structural Formula	Example No.	Structural Formula
1		6	
2		7	
3		8	
4		9	
5		10	

Table 4

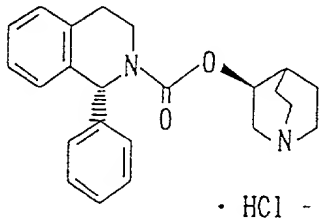
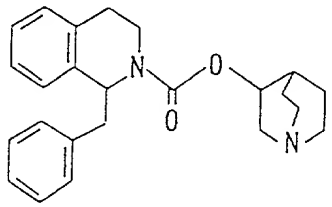
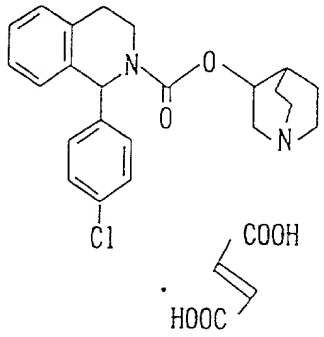
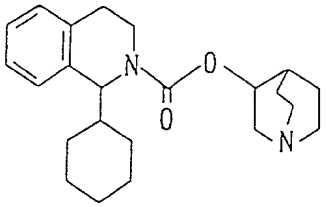
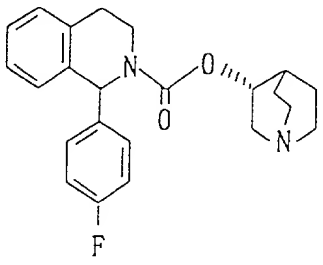
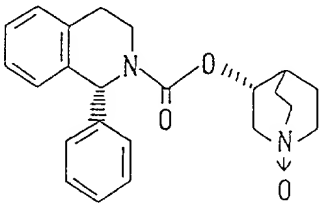
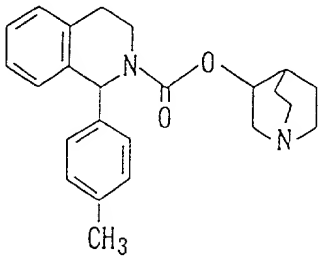
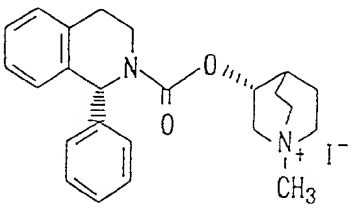
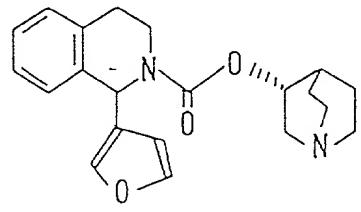
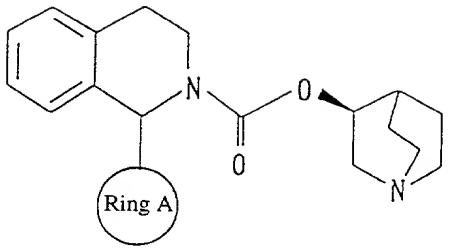
Example No.	Structural Formula	Example No.	Structural Formula
11		15	
12		16	
13		17	
14		18	

Table 5

Example No.	Structural Formula
19	

Each of the above-described compounds in Examples 3-6, 12-14, 16 and 19 can be obtained as an optical resolved form as shown in the following Tables 6-8 using an optically resolved intermediate in a similar manner to Examples 8-11.

Table 6



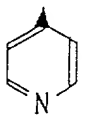
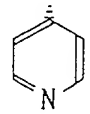
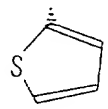
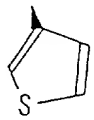
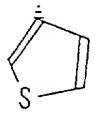
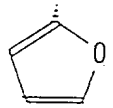
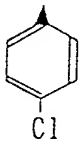
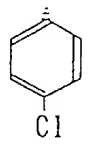
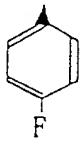
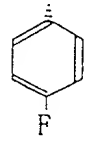
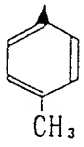
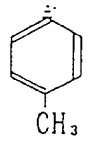
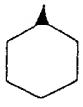
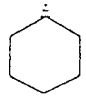
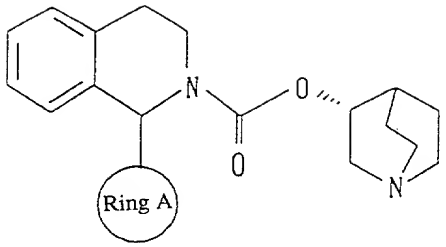
Example No.	Ring A	Example No.	Ring A
3-(a)		3-(b)	
4-(a)		4-(b)	
5-(a)		5-(b)	
6-(a)		6-(a)	
12-(a)		12-(b)	
13-(a)		13-(b)	
14-(a)		14-(b)	
16-(a)		16-(b)	

Table 7



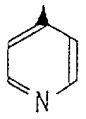
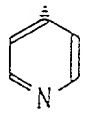
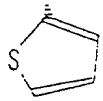
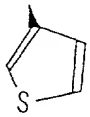
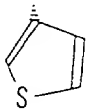
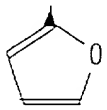
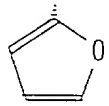
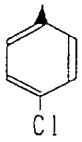
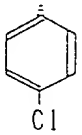
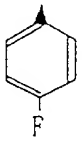
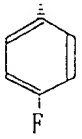
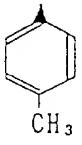
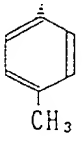
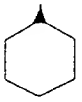
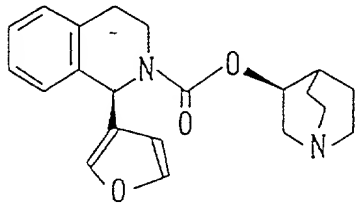
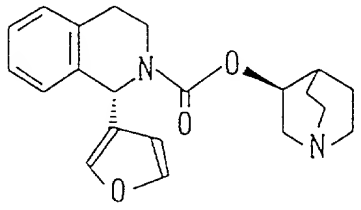
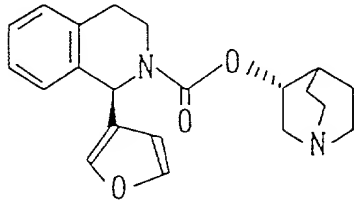
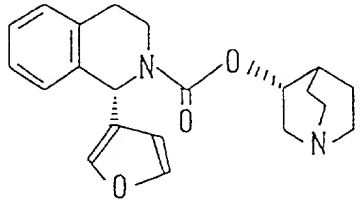
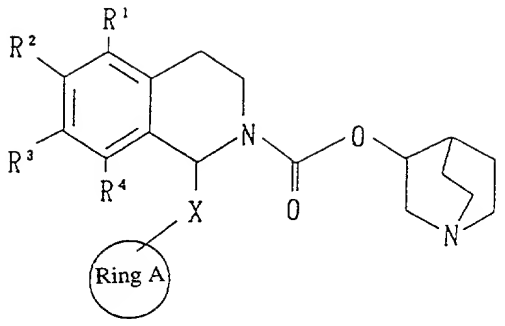
Example No.	Ring A	Example No.	Ring A
3-(c)		3-(d)	
4-(c)		4-(d)	
5-(c)		5-(d)	
6-(c)		6-(d)	
12-(c)		12-(d)	
13-(c)		13-(d)	
14-(c)		14-(d)	
16-(c)		16-(d)	

Table 8

Example No.	Structural Formula
19-(a)	
19-(b)	
19-(c)	
19-(d)	

The other compounds embraced by the present invention will be shown in Tables 9-33. They can be synthesized by any one of the above-described preparation processes, processes described in Examples or processes known to those skilled in the art and do not require any particular experiment. Incidentally, these compounds are described as a racemic compound, but optical active substances based on an asymmetric carbon is also included.

Table 9



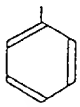
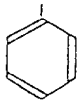
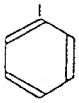
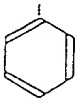
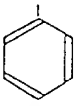
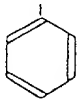
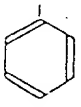
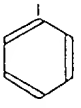
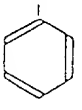
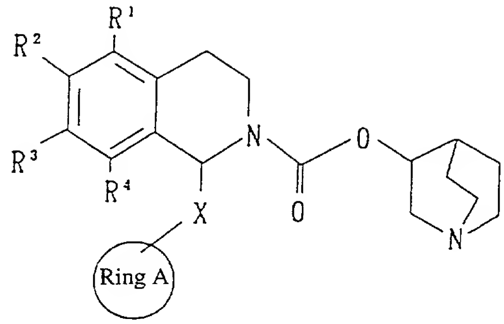
Compound No.	R 1	R 2	R 3	R 4	X	Ring A
A − 1	Cl	H	H	H	−	
A − 2	H	H	Cl	H	−	
A − 3	Cl	H	Cl	H	−	
A − 4	F	H	H	H	−	
A − 5	H	H	F	H	−	
A − 6	Br	H	H	H	−	
A − 7	H	H	Br	H	−	
A − 8	Cl	H	Br	H	−	
A − 9	CH_3	H	H	H	−	

Table 10



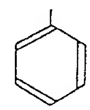
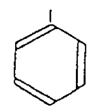
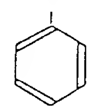
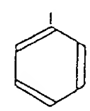
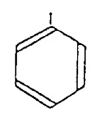
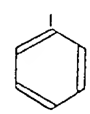
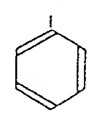
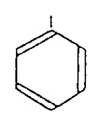
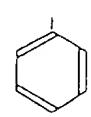
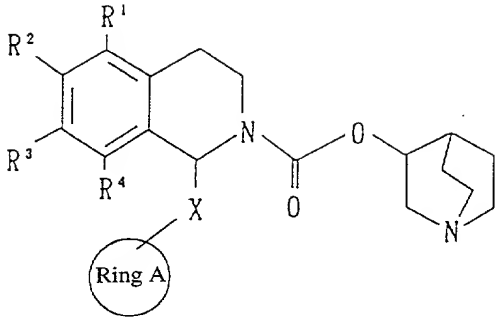
Compound No.	R¹	R²	R³	R⁴	X	Ring A
A－10	C_2H_5	H	H	H	－	
A－11	n-C_3H_7	H	H	H	－	
A－12	i-C_3H_7	H	H	H	－	
A－13	H	CH_3	H	H	－	
A－14	H	C_2H_5	H	H	－	
A－15	H	H	CH_3	H	－	
A－16	H	H	C_2H_5	H	－	
A－17	CH_3	H	CH_3	H	－	
A－18	H	CH_3	CH_3	H	－	

Table 11



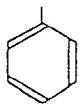
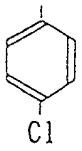
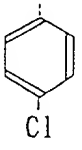
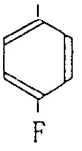
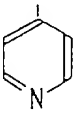
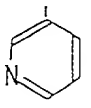
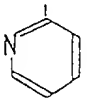
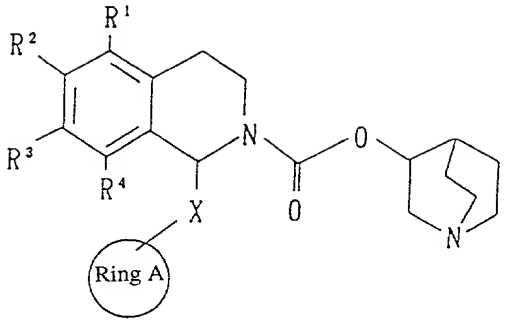
Compound No.	R 1	R 2	R 3	R 4	X	Ring A
A－19	CH_3	H	CH_3	CH_3	－	
A－20	Cl	H	H	H	－	
A－21	H	H	Cl	H	－	
A－22	H	H	Cl	H	－	
A－23	H	H	Cl	H	－	
A－24	H	H	Cl	H	－	
A－25	H	H	Cl	H	－	

Table 12



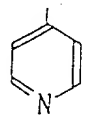
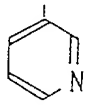
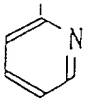
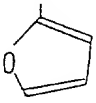
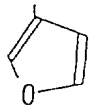
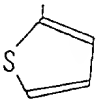
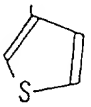
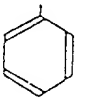
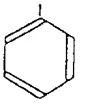
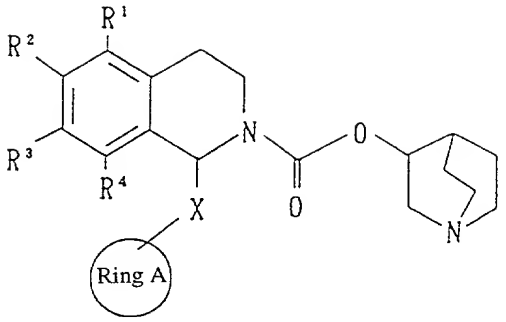
Compound No.	R 1	R 2	R 3	R 4	X	Ring A
A − 26	H	H	CH_3	H	−	
A − 27	Cl	H	H	H	−	
A − 28	H	CH_3	H	H	−	
A − 29	Cl	H	H	H	−	
A − 30	Cl	H	H	H	−	
A − 31	H	H	Cl	H	−	
A − 32	H	H	Cl	H	−	
A − 33	H	OCH_3	OCH_3	H	−	
A − 34	H	$-OCH_2O-$		H	−	

Table 13



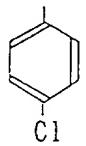
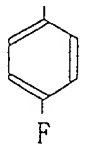
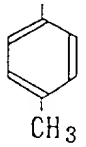
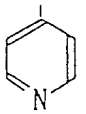
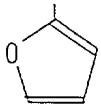
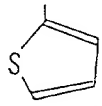
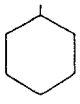
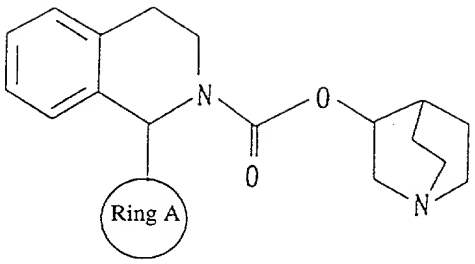
Compound No.	R 1	R 2	R 3	R 4	X	Ring A
A－35	H	H	H	H	CH_2	
A－36	H	H	H	H	CH_2	
A－37	H	H	H	H	CH_2	
A－38	H	H	H	H	CH_2	
A－39	H	H	H	H	CH_2	
A－40	Cl	H	H	H	CH_2	
A－41	Cl	H	H	H	CH_2	
A－42	Cl	H	H	H	CH_2	

Table 14



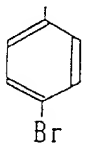
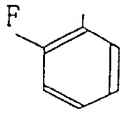
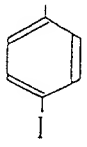
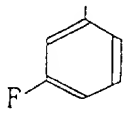
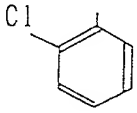
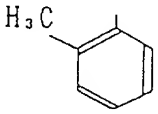
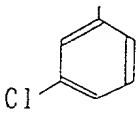
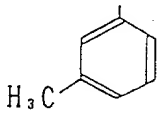
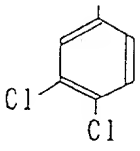
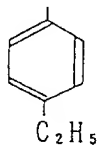
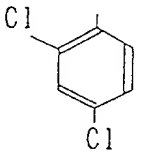
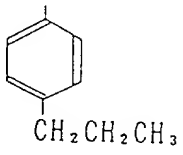
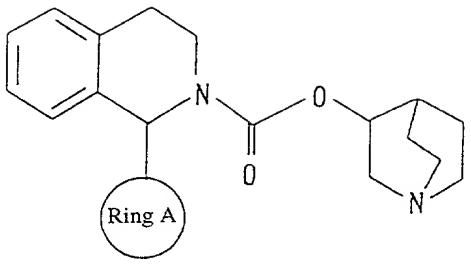
Compound No.	Ring A	Compound No.	Ring A
B − 1		B − 7	
B − 2		B − 8	
B − 3		B − 9	
B − 4		B − 10	
B − 5		B − 11	
B − 6		B − 12	

Table 15



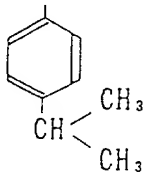
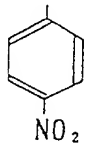
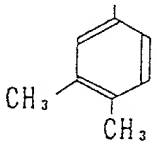
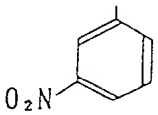
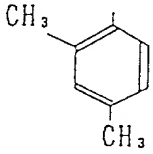
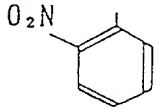
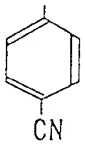
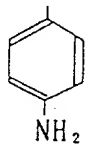
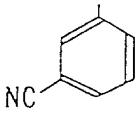
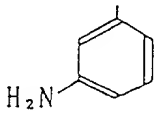
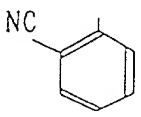
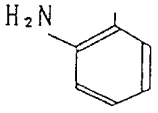
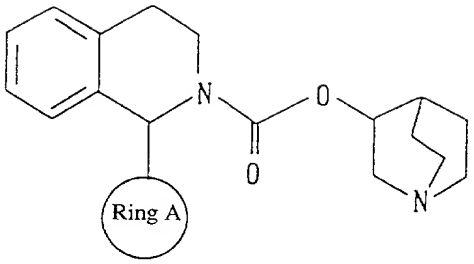
Compound No.	Ring A	Compound No.	Ring A
B－13		B－19	
B－14		B－20	
B－15		B－21	
B－16		B－22	
B－17		B－23	
B－18		B－24	

Table 16



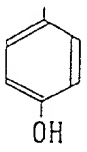
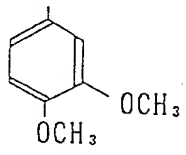
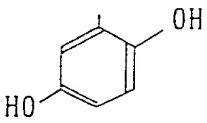
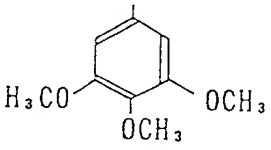
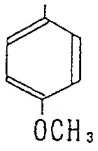
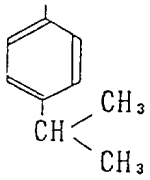
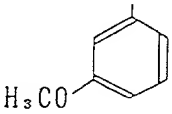
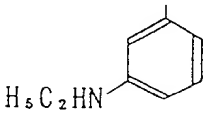
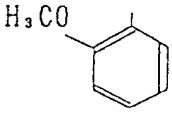
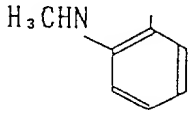
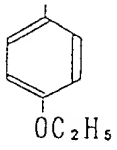
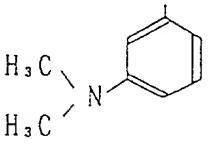
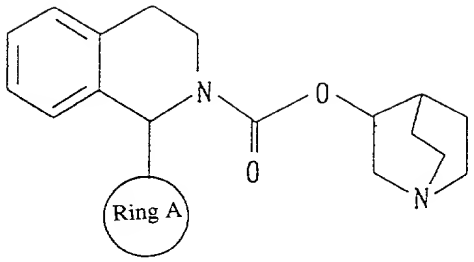
Compound No.	Ring A	Compound No.	Ring A
B – 25		B – 31	
B – 26		B – 32	
B – 27		B – 33	
B – 28		B – 34	
B – 29		B – 35	
B – 30		B – 36	

Table 17



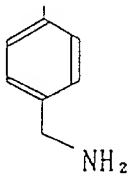
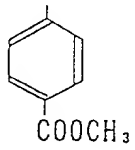
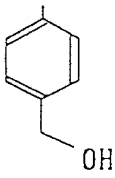
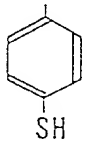
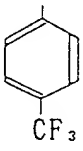
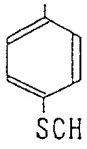
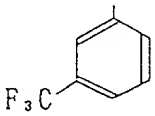
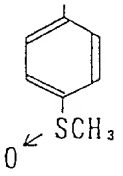
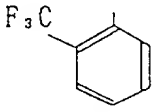
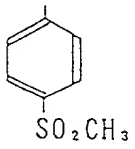
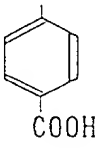
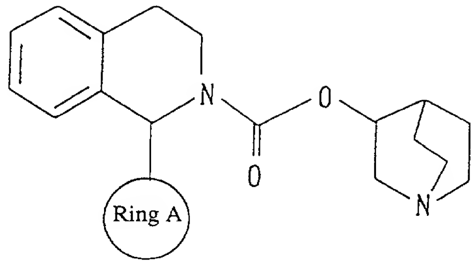
Compound No.	Ring A	Compound No.	Ring A
B－37		B－43	
B－38		B－44	
B－39		B－45	
B－40		B－46	
B－41		B－47	
B－42		B－48	

Table 18



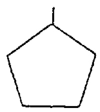
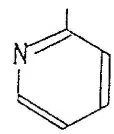
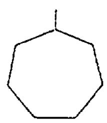
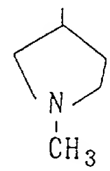
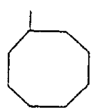
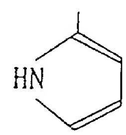
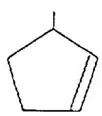
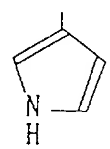
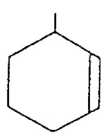
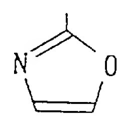
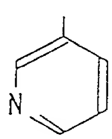
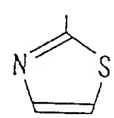
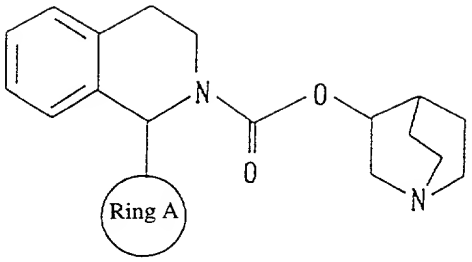
Compound No.	Ring A	Compound No.	Ring A
B − 49		B − 55	
B − 50		B − 56	
B − 51		B − 57	
B − 52		B − 58	
B − 53		B − 59	
B − 54		B − 60	

Table 19



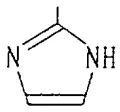
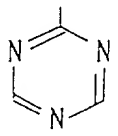
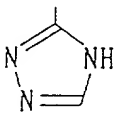
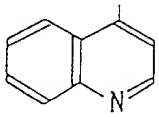
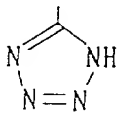
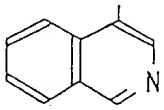
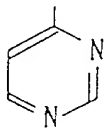
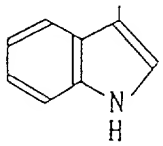
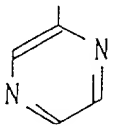
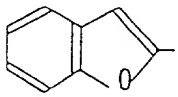
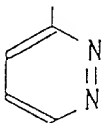
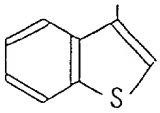
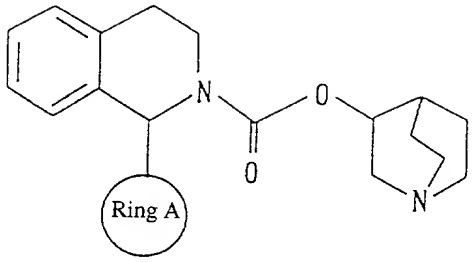
Compound No.	Ring A	Compound No.	Ring A
B – 61		B – 67	
B – 62		B – 68	
B – 63		B – 69	
B – 64		B – 70	
B – 65		B – 71	
B – 66		B – 72	

Table 20



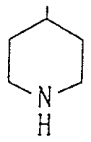
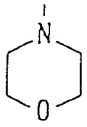
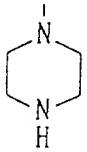
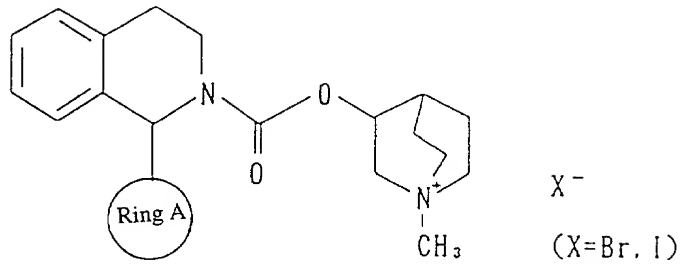
Compound No.	Ring A
B − 73	
B − 74	
B − 75	

Table 21



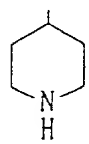
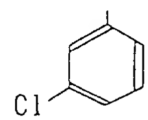
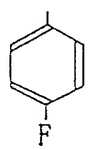
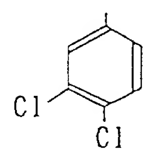
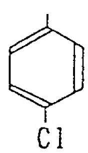
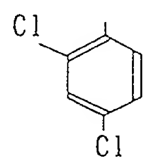
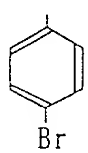
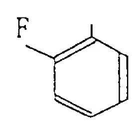
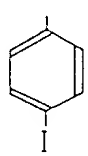
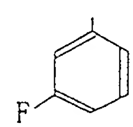
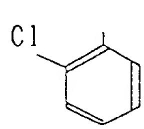
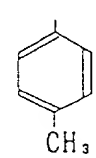
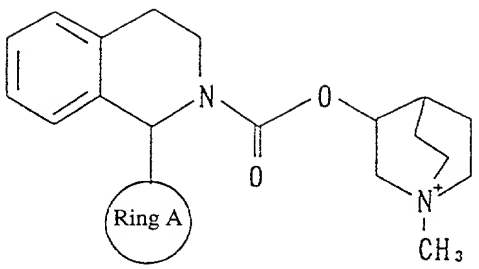
Compound No.	Ring A	Compound No.	Ring A
B − 76		B − 82	
B − 77		B − 83	
B − 78		B − 84	
B − 79		B − 85	
B − 80		B − 86	
B − 81		B − 87	

Table 22



X^-

(X=Br, I)

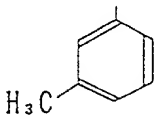
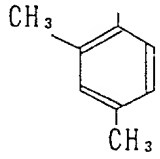
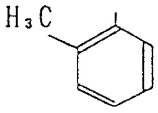
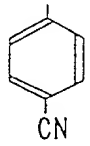
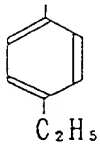
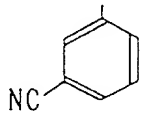
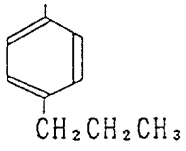
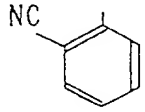
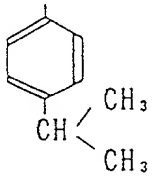
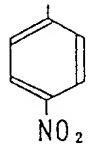
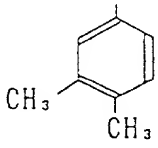
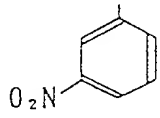
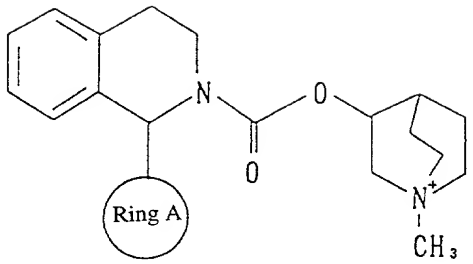
Compound No.	Ring A	Compound No.	Ring A
B－88		B－94	
B－89		B－95	
B－90		B－96	
B－91		B－97	
B－92		B－98	
B－93		B－99	

Table 23



X^-

(X=Br, I)

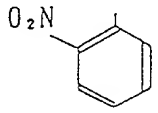
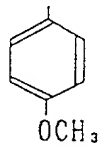
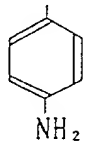
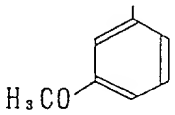
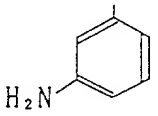
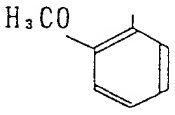
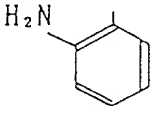
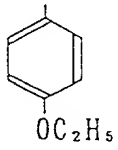
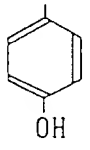
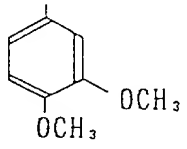
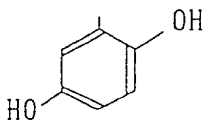
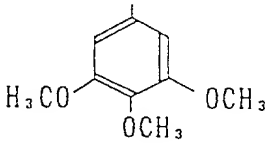
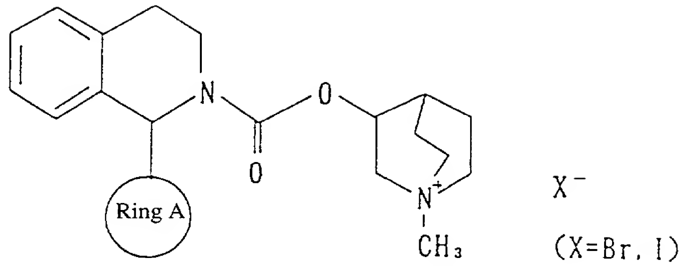
Compound No.	Ring A	Compound No.	Ring A
B-100		B-106	
B-101		B-107	
B-102		B-108	
B-103		B-109	
B-104		B-110	
B-105		B-111	

Table 24



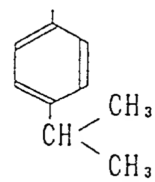
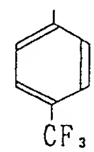
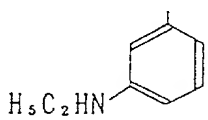
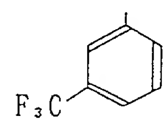
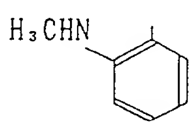
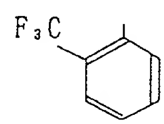
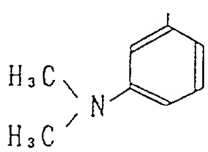
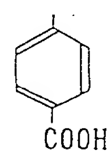
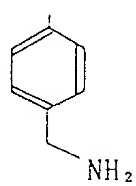
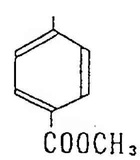
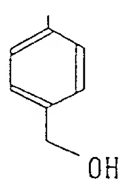
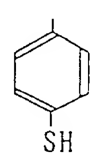
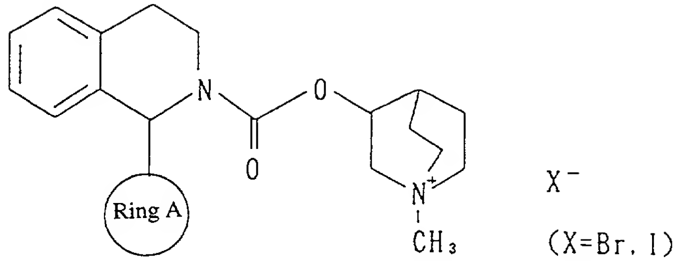
Compound No.	Ring A	Compound No.	Ring A
B-112		B-118	
B-113		B-119	
B-114		B-120	
B-115		B-121	
B-116		B-122	
B-117		B-123	

Table 25



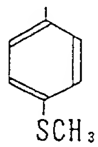
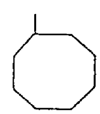
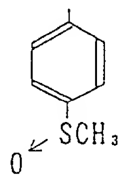
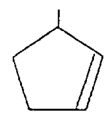
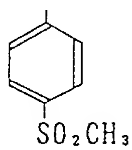
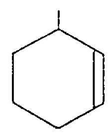
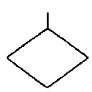
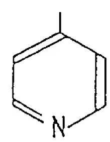
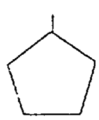
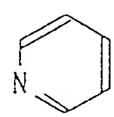
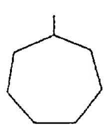
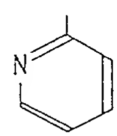
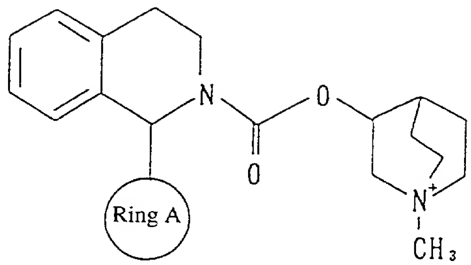
Compound No.	Ring A	Compound No.	Ring A
B-124		B-130	
B-125		B-131	
B-126		B-132	
B-127		B-133	
B-128		B-134	
B-129		B-135	

Table 26



X^-

(X=Br, I)

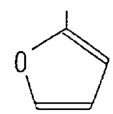
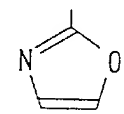
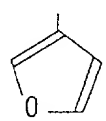
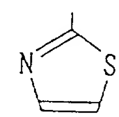
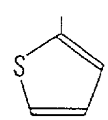
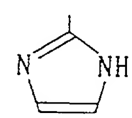
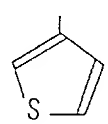
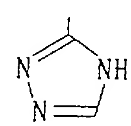
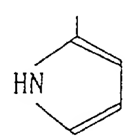
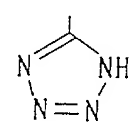
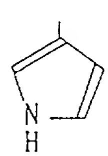
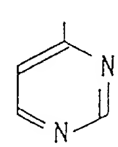
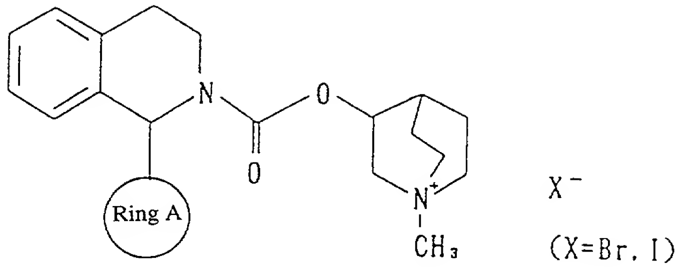
Compound No.	Ring A	Compound No.	Ring A
B-136		B-142	
B-137		B-143	
B-138		B-144	
B-139		B-145	
B-140		B-146	
B-141		B-147	

Table 27



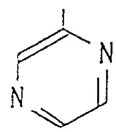
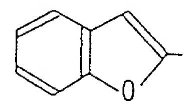
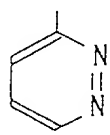
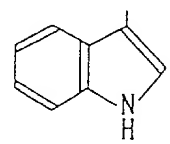
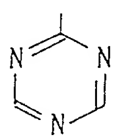
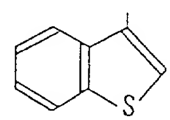
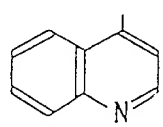
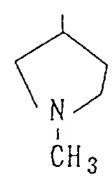
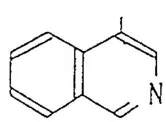
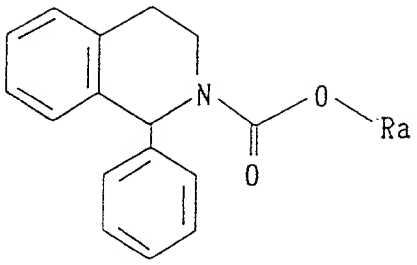
Compound No.	Ring A	Compound No.	Ring A
B-148		B-153	
B-149		B-154	
B-150		B-155	
B-151		B-156	
B-152			

Table 28



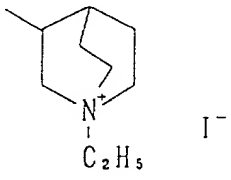
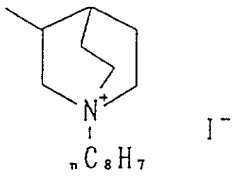
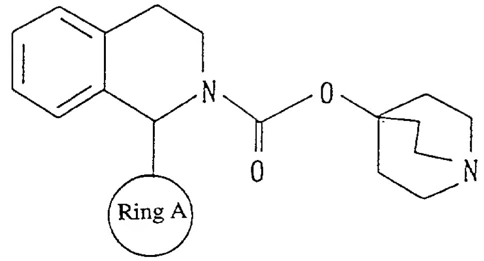
Compound No.	Ring A	Compound No.	Ring A
B-157		B-158	

Table 29



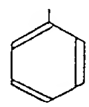
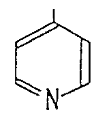
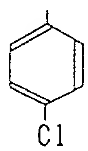
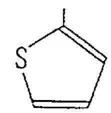
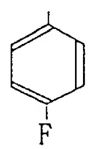
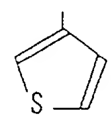
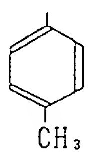
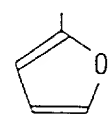
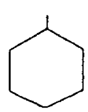
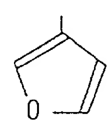
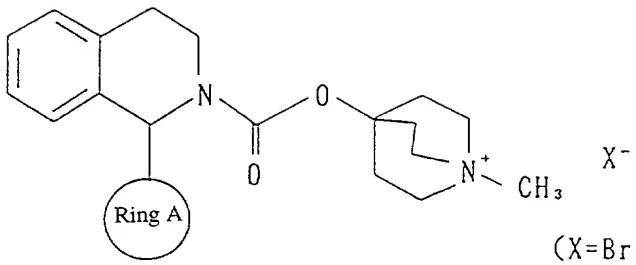
Compound No.	Ring A	Compound No.	Ring A
B-159		B-164	
B-160		B-165	
B-161		B-166	
B-162		B-167	
B-163		B-168	

Table 30



(X=Br. I)

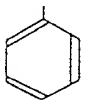
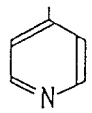
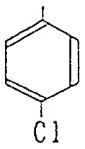
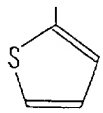
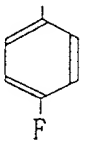
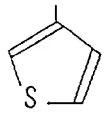
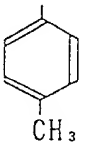
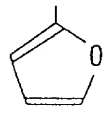
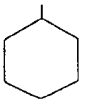
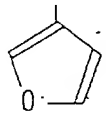
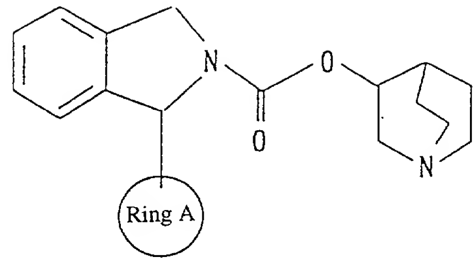
Compound No.	Ring A	Compound No.	Ring A
B-169		B-174	
B-170		B-175	
B-171		B-176	
B-172		B-177	
B-173		B-178	

Table 31



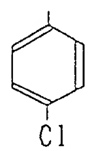
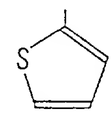
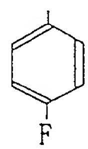
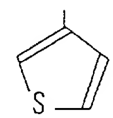
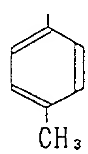
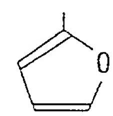
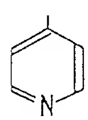
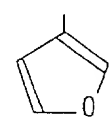
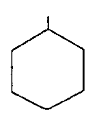
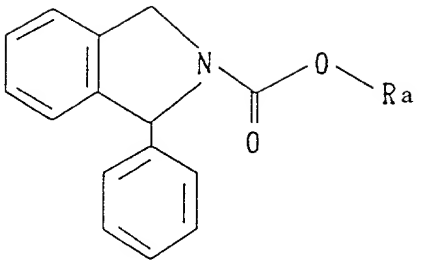
Compound No.	Ring A	Compound No.	Ring A
B-179		B-184	
B-180		B-185	
B-181		B-186	
B-182		B-187	
B-183			

Table 32



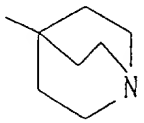
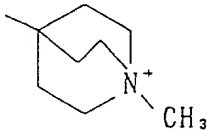
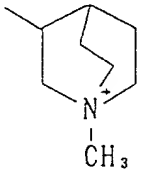
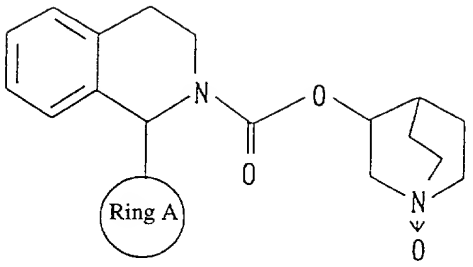
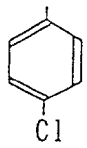
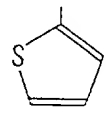
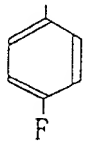
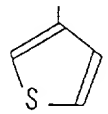
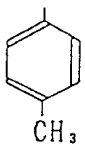
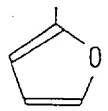
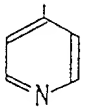
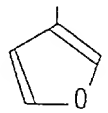
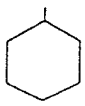
Compound No.	R_a
B-188	
B-189	 I^-
B-190	 I^-

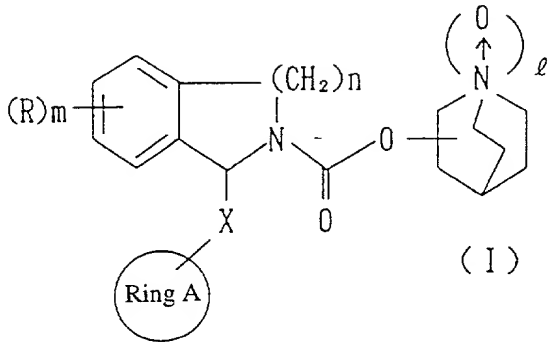
Table 33



Compound No.	Ring A	Compound No.	Ring A
B-191		B-196	
B-192		B-197	
B-193		B-198	
B-194		B-199	
B-195			

CLAIMS

1. A quinuclidine derivative represented by the following formula (I):



(I)

(symbols in the formula have the following meanings:

Ring A: an aryl group, a cycloalkyl group, a cycloalkenyl group, a heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, wherein said ring may be substituted by an optional substituent;

X: a single bond or a methylene group;

R: a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower

alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group or a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group;

ℓ: 0 or 1,

m: 0 or an integer of 1 to 3, and

n: an integer of 1 or 2),

a salt thereof, an N-oxide thereof, or a quaternary ammonium salt thereof.

2. The quinuclidine derivative, a salt thereof, an N-oxide thereof or a quaternary ammonium salt thereof according to claim 1, wherein the ring A represents an aryl group, a cycloalkyl group, a cycloalkenyl group, an heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, in which said ring may be substituted by a substituent selected from the group consisting of a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower

alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group, and a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group.

3. The quinuclidine derivative, a salt thereof, an N-oxide thereof or a quaternary ammonium salt thereof according to claim 2, wherein R represents a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group, a nitro group, a cyano group, an amino group or a mono- or di-lower alkylamino group, and the ring A represents an aryl group, a cycloalkyl group, a cycloalkenyl group, a 5- or 6-membered monocyclic heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, in which said ring may be substituted by a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group, a nitro group, a cyano group, an amino group or a mono- or di-lower alkylamino group.

4. The quinuclidine derivative, a salt thereof, an N-oxide thereof or a quaternary ammonium salt thereof

according to claim 3, wherein m is 0, and the ring A represents an aryl group, a cycloalkyl group or a cycloalkenyl group which may be substituted by a halogen atom, a lower alkyl group, a hydroxyl group or a lower alkoxy group, or a 5- or 6-membered monocyclic heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom.

5. The quinuclidine derivative, a salt thereof, an N-oxide thereof or a quaternary ammonium salt thereof according to claim 4, wherein the ring A represents a phenyl group which may be substituted by a halogen atom or a lower alkyl group, a cycloalkyl group, a pyridyl group, a furyl group or a thienyl group.

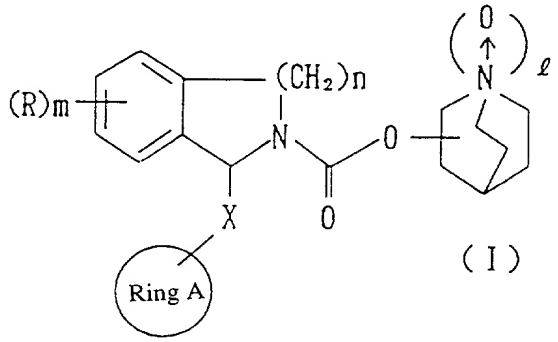
6. The quinuclidine derivative, a salt thereof, an N-oxide thereof or a quaternary ammonium salt thereof according to any one of claims 2 to 5, wherein X represents a single bond.

7. The quinuclidine derivative, a salt thereof, an N-oxide thereof or a quaternary ammonium salt thereof according to any one of claims 2 to 6, wherein n is 2.

8. A quinuclidine derivative, a salt thereof, an N-oxide thereof or a quaternary ammonium salt thereof according to any one of claim 1, which is selected from the group consisting of 3-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 3-quinuclidinyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate,

3-quinuclidinyl 1,2,3,4-tetrahydro-1-(2-thienyl)-2-isoquinolinecarboxylate, 3-quinuclidinyl 1,2,3,4-tetrahydro-1-(3-thienyl)-2-isoquinolinecarboxylate, 3-quinuclidinyl 1-(2-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 3-quinuclidinyl 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 3-quinuclidinyl 1-(4-fluorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 3-quinuclidinyl 1,2,3,4-tetrahydro-1-(4-tolyl)-2-isoquinolinecarboxylate, 3-quinuclidinyl 1-cyclohexyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 3-quinuclidinyl 1-(3-furyl)-1,2,3,4-tetrahydro-2-isoquinoline carboxylate, and optically active substances thereof.

9. A pharmaceutical composition which comprises a quinuclidine derivative represented by the following formula (I):



(I)

(symbols in the formula have the following meanings:

Ring A: an aryl group, a cycloalkyl group, a cycloalkenyl group, a heteroaryl group having

1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, wherein said ring may be substituted by an optional substituent;

X: a single bond or a methylene group;

R: a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group or a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group;

ℓ: 0 or 1,

m: 0 or an integer of 1 to 3, and

n: an integer of 1 or 2, or

a salt thereof, an N-oxide or a quaternary ammonium salt thereof,

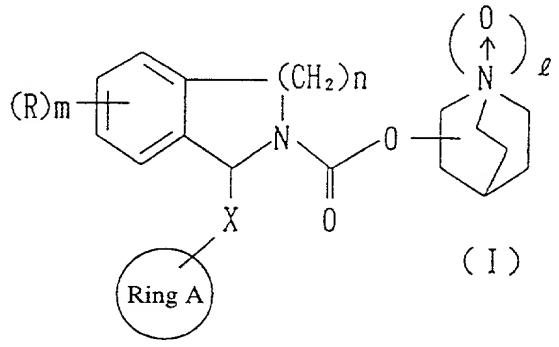
and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition according to claim 9, which is a muscarinic M_3 receptor antagonist.

11. A pharmaceutical composition according to claim 10, wherein the muscarinic M_3 receptor antagonist is an agent for prevention/treatment of urinary diseases (urinary incontinence or pollakiuria in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm or chronic cystitis) or respiratory diseases (chronic obstructive pulmonary diseases, chronic bronchitis, asthma or rhinitis).

ABSTRACT

Quinuclidine derivatives represented by general following general formula (I), salts, N-oxides or quaternary ammonium salts thereof, and medicinal compositions containing the same.



(I)

The compound has an antagonistic effect on muscarinic M_3 receptors and is useful as a preventive or remedy for urologic diseases, respiratory diseases or digestive diseases.

PCT

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name: that I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural names are listed below) of the subject matter claimed and for which a patent is sought in the application entitled:

NOVEL QUINUCLIDINE DERIVATIVES AND MEDICINAL COMPOSITION THEREOF

which application is:
☐ the attached application *(for original application)*

☒ application Serial No. 08/860,377 .
filed June 25, 1997, and amended on

(for declaration not accompanying application)

that I have reviewed and understand the contents of the specification of the above-identified application, including the claims, as amended by any amendment referred to above; that I acknowledge my duty to disclose information of which I am aware and which is material to the examination of this application under 37 C.F.R. 1.56; and that I hereby claim foreign priority benefits under Title 35, United States Code §119, §172 or §365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified on said list any foreign application for patent or inventor's certificate on this invention having a filing date before that of the application on which priority is claimed:

Application Number	Country	Filing Date	Priority Claimed (yes or no)
Pat. Hei-6-327045	Japan	December 28, 1994	yes

I hereby claim the benefit of Title 35, United States Code §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in a listed prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge my duty to disclose any material information under 37 C.F.R. 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (patented, pending, abandoned)

I hereby appoint John H. Mion, Reg. No. 18,879; Donald E. Zinn, Reg. No. 19,046; Thomas J. Macpeak, Reg. No. 19,292; Robert J. Seas, Jr., Reg. No. 21,092; Darryl Mexic, Reg. No. 23,063; Robert V. Sloan, Reg. No. 22,775; Peter D. Olexy, Reg. No. 24,513; J. Frank Osha, Reg. No. 24,625; Waddell A. Biggart, Reg. No. 24,861; Robert G. McMorrow, Reg. No. 19,093; Louis Gubinsky, Reg. No. 24,835; Neil B. Siegel, Reg. No. 25,200; David J. Cushing, Reg. No. 28,703; John R. Inge, Reg. No. 26,916; Joseph J. Ruch, Jr., Reg. No. 26,577; Sheldon I. Landsman, Reg. No. 25,430; Richard C. Turner, Reg. No. 29,710; Howard L. Bernstein, Reg. No. 25,665; Alan J. Kasper, Reg. No. 25,426; Kenneth J. Burchfiel, Reg. No. 31,333; Gordon Kit, Reg. No. 30,764; Susan J. Mack, Reg. No. 30,951; Frank L. Bernstein, Reg. No. 31,484; Mark Boland, Reg. No. 32,197; William H. Mandir, Reg. No. 32,156; Scott M. Daniels, Reg. No. 32,562; and Brian W. Hannon, Reg. No. 32,778, my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and request that all correspondence about the application be addressed to SUGHRUE, MION, ZINN, MACPEAK & SEAS, 2100 Pennsylvania Avenue, N.W., Washington, D.C. 20037.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date July 28, 1997

First Inventor Makoto -- TAKEUCHI
(First Name / Middle Initial / Last Name)

Residence Ibaraki, Japan JPX

Signature Makoto Takeuchi

Citizenship Japan

Post Office Address 9-14, Matsumaedai 7-chome, Moriya-machi, Kitasoumagun, Ibaraki 302-01 Japan

---

Date July 28, 1997

Second Inventor Ryo -- NAITO
(First Name / Middle Initial / Last Name)

Residence Ibaraki, JPX Japan

Signature Ryo Naito

Citizenship Japan

Post Office Address 15-23-102, Hanabatake 3-chome, Tsukuba-shi, Ibaraki 300-32 Japan

Date July 28, 1997 3:00

3rd Inventor Masahiko -- HAYAKAWA
First Name Middle Initial Last Name

Residence Ibaraki, JPX

Signature Masahiko Hayakawa

Japan

Post Office Address 5-9-424, Ninomiya 2-chome,

Citizenship Japan

Tsukuba-shi, Ibaraki 305 Japan

Date July 28, 1997 4:00

4th Inventor Yoshinori -- OKAMOTO
First Name Middle Initial Last Name

Residence ~~Ibaraki~~ JPX

Signature Yoshinori Okamoto

Japan

Post Office Address 5-9-207, Ninomiya 2-chome,

Citizenship Japan

Tsukuba-shi, Ibaraki 305 Japan

Date July 28, 1997 5:00

5th Inventor Yasuhiro -- YONETOKU
First Name Middle Initial Last Name

Residence Ibaraki, JPX

Signature Yasuhiro Yonetoku

Japan

Post Office Address 5-9-423, Ninomiya 2-chome,

Citizenship Japan

Tsukuba-shi, Ibaraki 305 Japan

Date July 28, 1997 6:00

6th Inventor Ken -- IKEDA
First Name Middle Initial Last Name

Residence Chiba, JPX

Signature Ken Ikeda

Japan

Post Office Address 2-25-106, Tsukushino 1-chome,

Citizenship Japan

Abiko-shi, Chiba 270-11 Japan

Date July 28, 1997 7:00

7th Inventor Yasuo -- ISOMURA
First Name Middle Initial Last Name

Residence Ibaraki, JPX

Signature Yasuo Isomura

Japan

Post Office Address 4-8, Yakushidai 3-chome,

Citizenship Japan

Moriya-machi, Kitasoumagun,
Ibaraki 302-01 Japan

Date

8th Inventor
First Name Middle Initial Last Name

Residence

Signature

Post Office Address

Citizenship